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Research Submissions

Open-Label, Multi-Dose, Pilot Safety Study of Injection of OnabotulinumtoxinA Toward the Otic Ganglion for the Treatment of Intractable Chronic Cluster Headache

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Background.—The otic ganglion (OG) provides parasympathetic innervation to the cerebral circulation and cranial structures and may be involved in the pathophysiology of trigeminal autonomic headaches. This structure has never been targeted in any headache disorder.

Objective.—To investigate the safety of injecting onabotulinumtoxin A (BTA) toward the OG in 10 patients with intractable chronic cluster headache and to collect efficacy data.

Methods.—A total of 10 patients with chronic cluster headache were enrolled in this open-label, multi-dose pilot safety study. All patients were recruited and treated on an out-patient basis at St Olav's University Hospital (Norway). In 5 patients each, the OG was the injection target with 12.5 IU of BTA or 25 IU, respectively. The primary outcome measure was adverse events (AEs) and the main secondary outcome was the number of attacks per week measured at baseline and in the second month following injection.

Results.—For the primary endpoint, we analyzed data for all 10 patients. There were a total of 17 AEs in 6 of the 10 patients. All AEs were considered mild and disappeared by the end of follow-up. The median number of attacks per week at baseline was 17.0 [7.8 to 25.8] vs 14.0 [7.3 to 20.0] in the second month following injection; difference: 3 (95%CI: −0.3 to 7.9), $P = .063$.

Conclusions.—Injection with BTA toward the OG appears to be safe. We did not find a statistically significant reduction in the number of attacks per week at month 2 after injection compared to the baseline. This study suggests that the OG is not an important target for the treatment of chronic cluster headache. A future study employing more precise targeting of the OG may be indicated.

Key words: chronic cluster headache, otic ganglion, sphenopalatine ganglion, pterygopalatine ganglion, botulinum toxin, trigeminal autonomic cephalalgia

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Abbreviations: CH cluster headache., CT computerized tomography, ICHD-3 International Classification of Headache Disorders, third edition, MRI magnetic resonance imaging, OG otic ganglion, SD standard deviation, SPG sphenopalatine ganglion

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INTRODUCTION

The otic ganglion (OG) has been introduced as a possible target in trigeminal autonomic cephalalgias.[1] Cluster headache (CH) is the most common of the trigeminal autonomic cephalalgias[2,3] with a significant impact on the sufferer's quality of life and no approved treatments for its chronic form.[4]

A "loop" from the trigeminocervical complex to the dural blood vessels has been described.[5] The afferent part of this loop sends nociceptive signals from the dural blood vessels to the trigeminocervical complex. This information projects to higher brain structures, resulting in cephalic pain. The efferent pathway of this trigeminal autonomic reflex is considered to originate in the superior salivatory nucleus with efferents exiting the brain stem via the facial nerve and reaching the sphenopalatine ganglion (SPG) through the greater petrosal nerve. Postganglionic fibers exit the sphenopalatine nerve toward the dural vessels, closing a loop which is thought to be crucial in pathophysiology of the trigeminal autonomic cephalalgias.[5] This has been rational to target the SPG in several headache disorders.[6]

It has been hypothesized that the trigeminal autonomic reflex loop is more complex than previously thought.[1] The efferent part of this loop, in addition to the projections toward the SPG, might involve another efferent pathway; fibers from the inferior salivatory nucleus, which project to the OG. The OG is a small structure (approximately 4 mm long, 3 mm wide, and 1.5 mm thick) located in the infratemporal fossa[7] (Fig. 1). Its location and relationship to adjacent structures appear to be constant.[8] It is situated directly medial to and in contact with the mandibular nerve.[8] The mean distance from the OG to the foramen ovale (a structure localizable on head computed tomography (CT) scans) is 4.5 mm (SD 1.7).[1] Some important nearby structures are the middle meningeal artery, maxillary

Conflict of Interest: Dr. Crespi has nothing to disclose. Dr. Bratbak is a co-inventor of a patented device used to perform the treatment and may benefit financially from a commercialization of the device. Dr. Matharu serves on the advisory board for Abbott, Allergan, Autonomic Technologies Inc, Eli Lilly, Medtronic, Novartis and TEVA, and has received payment for the development of educational presentations from Abbott, Allergan, Medtronic and electroCore. David W. Dodick reports the following conflicts: Personal fees: Amgen, AEON, Association of Translational Medicine, University Health Network, Daniel Edelman Inc, Autonomic Technologies, Axsome, Aural Analytics, Allergan, Alder BioPharmaceuticals, Biohaven, Charleston Laboratories, Clexio, Dr. Reddy's Laboratories/ Promius, Electrocore LLC, Eli Lilly, eNeura, Neurolief, Novartis, Ipsen, Impel, Satsuma, Supernus, Sun Pharma (India), Theranica, Teva, Vedanta, WL Gore, Nocira, PSL Group Services, University of British Columbia, XoC, Zosano, ZP Opco, Foresite Capital, Oppenheimer; Upjohn (Division of Pfizer), Pieris, Revance, Equinox, Salvia, Amzak Health. Speaking fees: Eli Lilly, Novartis Canada, Amgen. Speakers Bureaus: None. CME fees or royalty payments: HealthLogix, Medicom Worldwide, MedLogix Communications, Mednet, Miller Medical, PeerView, WebMD Health/Medscape, Chameleon, Academy for Continued Healthcare Learning, Universal Meeting Management, Haymarket, Global Scientific Communications, Global Life Sciences, Global Access Meetings, UpToDate (Elsevier), Oxford University Press, Cambridge University Press, Wolters Kluwer Health; Stock options: Precon Health, Aural Analytics, Healint, Theranica, Second Opinion/Mobile Health, Epien, Nocira, Matterhorn/Ontologics, King-Devick Technologies; Consulting without fee: Aural Analytics, Healint, Second Opinion/Mobile Health, Epien; Board of Directors: Epien, Matterhorn/ Ontologics, King-Devick Technologies. Patent: 17189376.1-1466:vTitle: Botulinum Toxin Dosage Regimen for Chronic Migraine Prophylaxis without fee; Research funding: American Migraine Foundation, US Department of Defense, PCORI, Henry Jackson Foundation; Professional society fees or reimbursement for travel: American Academy of Neurology, American Brain Foundation, American Headache Society, American Migraine Foundation, International Headache Society, Canadian Headache Society. Dr. Gulati, Dr. Solheim and Dr.. Berntsen have nothing to disclose. Dr. Tronvik may benefit financially from the commercialization of the device.

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The trial was registered in the EUDRACT database: 2016-004213-28 and at ClinicalTrials.gov (NCT03066635).

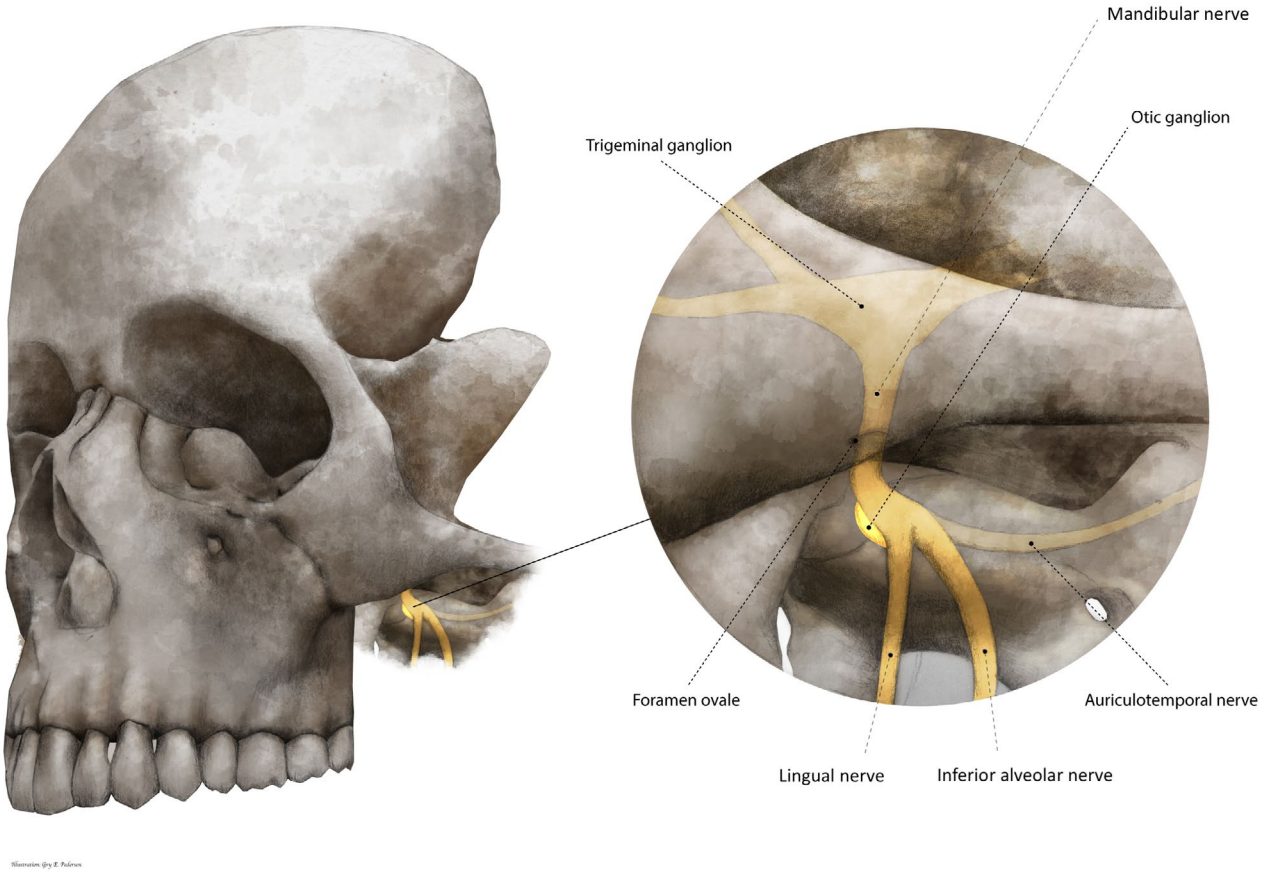

Fig. 1.—Location of the otic ganglion (OG) in the infratemporal fossa.

artery, lingual nerve, and inferior alveolar nerve. The preganglionic parasympathetic fibers originate in the inferior salivatory nucleus, exit the brain stem via the glossopharyngeal nerve, then travel with the tympanic nerve, the lesser petrosal nerve, and synapse in the OG. Some postganglionic fibers exit the ganglion toward the auriculotemporal nerve and reach the parotid gland. Other fibers leave the ganglion via the external sphenoidal nerve (also referred to as dorsal rami, ganglionic cord, internal sphenoidal nerve or rami communicantes cum sinus cavernosus).[8] These fibers reach the trigeminal ganglion and ganglia of the cavernous sinus. This parasympathetic innervation of intracranial vessels from the OG has been shown in animal models[9-11] and humans.[12,13] Nociceptive fibers come in very close contact with parasympathetic and sympathetic fibers in the cavernous sinus.[14] The cavernous sinus has been proposed to have a central role in cluster headache pathophysiology[15] and cluster headache-like attacks have been reported in patients with lesions affecting the cavernous sinus.[16,17] It has been described that approximately 50% of the cranial vasomotor response is mediated by the OG and the other 50% by the SPG in an animal model.[18] Parasympathetic fibers synapse in the OG.[8] Histological analysis of the human OG is positive for choline acetyltransferase (unpublished work of Prof. Angelov at the Anatomical Institute of the University of Cologne, Germany). BTA blocks the release of acetylcholine. We hypothesize that BTA can produce a selective parasympathetic block in the OG.

The main objective of this pilot study was to investigate the safety of injecting 2 different doses of BTA toward the OG in 10 patients with intractable chronic CH. Efficacy data were also collected in order to determine whether future placebo-controlled studies are warranted.

METHOD

Study Design and Participants.—The study was designed as an open-label, multi-dose pilot safety study.

Among 11 patients screened for inclusion, 1 patient was ineligible and did not have enough attacks at the baseline to be included in this open-label trial. A total of 10 patients with chronic cluster headache (ICDH-3 beta criteria) were recruited and treated between June 2017 and May 2019 at St Olavs University Hospital, Trondheim (Norway). The study had only 1 site.

The inclusion and exclusion criteria are presented in Supplementary Table 1. "Moderate intractability" in CH has been defined as failing at least 2 drugs.[19] For this study, we defined intractability as having had unsatisfactory effect, intolerable side effects or contraindication of at least 2 of the following medications: suboccipital steroid injection, verapamil or lithium.

All 10 patients were examined by a neurologist. CT and MR scans were obtained before injection. CT scans were performed on a helical CT scanner (Siemens' Somatom sensation 64, Germany). MR images were performed on a 3 Tesla scanner (MAGNETOM Skyra, Siemens, Germany). Patients had to keep headache diaries 4 weeks prior to injection (baseline) and 6 months after injection recording adverse events (AEs), number of attacks, duration, intensity (0: no headache, 1: mild, 2: moderate, 3: strong, 4: unbearable), autonomic symptoms, triptan doses, and the use of oxygen. We defined a month as 28 days starting the day after treatment.

Description of the Procedure.—Our research group has developed a novel injection device to perform a surgical navigation-assisted administration of BTA toward the SPG (Fig. 2). This device (MultiGuide) has also been used in pilot trials in intractable chronic cluster headache,[20] chronic migraine,[21] and classic trigeminal neuralgia.[22] A single treatment was performed on an awake participant, using local anesthesia, in an outpatient office-based setting using a percutaneous approach and aided by surgical navigation (Brainlab Kick version 1, Brainlab AG, Feldkirchen, Germany). Surgical navigation is a system that tracks and displays the tip of an instrument relative to a pre-acquired medical image. MultiGuide enables the use of surgical navigation for high-precision injections. Pre-treatment planning of CT and MRI was performed with Brainlab iPlan 3.0 (Brainlab AG, Feldkirchen, Germany). The OG ipsilateral to the pain was localized directly medial to the mandibular nerve (nerve seen in MRI) and 4.5 mm inferior to the foramen ovale (seen in CT-scans; Fig. 3). With the patient in a supine position, the skin and deep structures toward the infratemporal fossa were anesthetized with 5-7 mL Marcaine-Adrenalin (5 mg/mL-5 μg/mL, AstraZeneca, Norway) and a 1-2 mm skin incision was made. Aided by surgical navigation and MultiGuide, 12.5 international units (IU) of BTA in 5 patients and 25 IU of BTA in 5 patients, suspended in 0.5 mL of isotonic saline were injected toward the OG ipsilateral to the pain. No previous studies have injected BTA toward the OG. We based the dose used in this study on previous trials that have injected BTA toward other cranial autonomic ganglia, that is, the SPG,[20-22] where both 25 and 50 IU BTA have been used. The reason why we used lower doses of BTA compared to previous trials targeting the SPG is that the OG has a smaller size, it has never been targeted before and that in the pilot trial targeting the SPG where both 25 and 50 IU BTA were tested, it did not appear to add any clinical benefit to use a dose higher than 25 IU.[20] The estimated duration of the injection was around 5 minutes and for the whole procedure including navigation system setup 30 minutes.

Outcome and Statistical Analysis.—The primary outcome was the development of AEs over the follow-up period of 6 months (or longer if needed). AEs were collected in a paper-pencil headache diary and in the case report form. Patients could report any symptom/discomfort that might be an AE to the

Table 1.—Demographics of the Sample

Number of screened patients	11
Number of included patients	10
Number of females/males	5/5
Mean age, years ± SD (range)	55.3 ± 12.6 (min 25-max 69)
Mean years with CH ± SD (range)	8.8 ± 10.0 (min 2-max 35)
Mean years with chronic CH ± SD (range)	4.9 ± 4.4 (min 1-max 14)
Number of Caucasians	10 out of 10
Side left/right	5/5
Topography	
Orbital	9 out of 10
Supraorbital	2 out of 10
Temporal	6 out of 10
Previous history of hypertension	3 out of 10
Previous history of depression	2 out of 10

CH = cluster headache; SD = standard deviation.

Fig. 2.—The MultiGuide, a novel injection device to perform surgical navigation-assisted procedures.

study investigators at any time during follow-up. A serious adverse event (SAE) is any AE that fulfills any of these criteria: (1) results in death; (2) is life threatening (this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it had been more severe); (3) requires inpatient hospitalization or prolongation of more than 24 hours of existing hospitalization; (4) results in persistent or significant disability/incapability; (5) produces a congenital anomaly/birth defect; (6) requires intervention to prevent permanent impairment or damage; (7) is medically important (refers to an event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent any of the SAEs defined above). Examples of medically important events are intensive treatment in an emergency room for allergic bronchospasm or blood dyscrasias, convulsions that do not result in hospitalization, development of drug dependency or drug abuse.

Planned hospitalization or surgical interventions for a condition that existed before the subject signed the informed consent form and did not change in severity are not SAEs. There was no disagreement between team members on the definition on SAEs.

The main secondary outcome was the number of attacks in month 2 after injection compared to baseline. A treatment responder was pre-defined as at least 50% reduction in the mean number of CH attacks per week between baseline and month 2 after injection. Other secondary outcomes were: CH attack duration, maximal pain intensity, presence of autonomic symptoms, triptan doses, use of oxygen, days without attacks, headache severity index, number of severe attacks (intensity 3 or 4 in a 0 to 4 point scale), and HIT-6 questionnaire. A scale developed to screen for cranial autonomic parasympathetic symptoms (CAPS scale) was administered at baseline and 1 and 6 months after injection.[23] Efficacy outcomes were measured on a paper-pencil diary at month 2 (predefined in protocol) since the onset of efficacy may require up to 4 weeks and maximal benefit would be expected during the second month before the usual attenuation of the effect of BTA during the third month after treatment. Other pilot trials with a similar design using BTA toward the SPG have also measured efficacy outcomes at month 2 because of the same reason.[20-22] Pain directly after injection and 1 day after was recorded on a numeric rating scale (NRS) from 0 to 10.

A protocol violator was defined as a participant with less than 80% of diary days registered or change in prophylactic medication during the study.

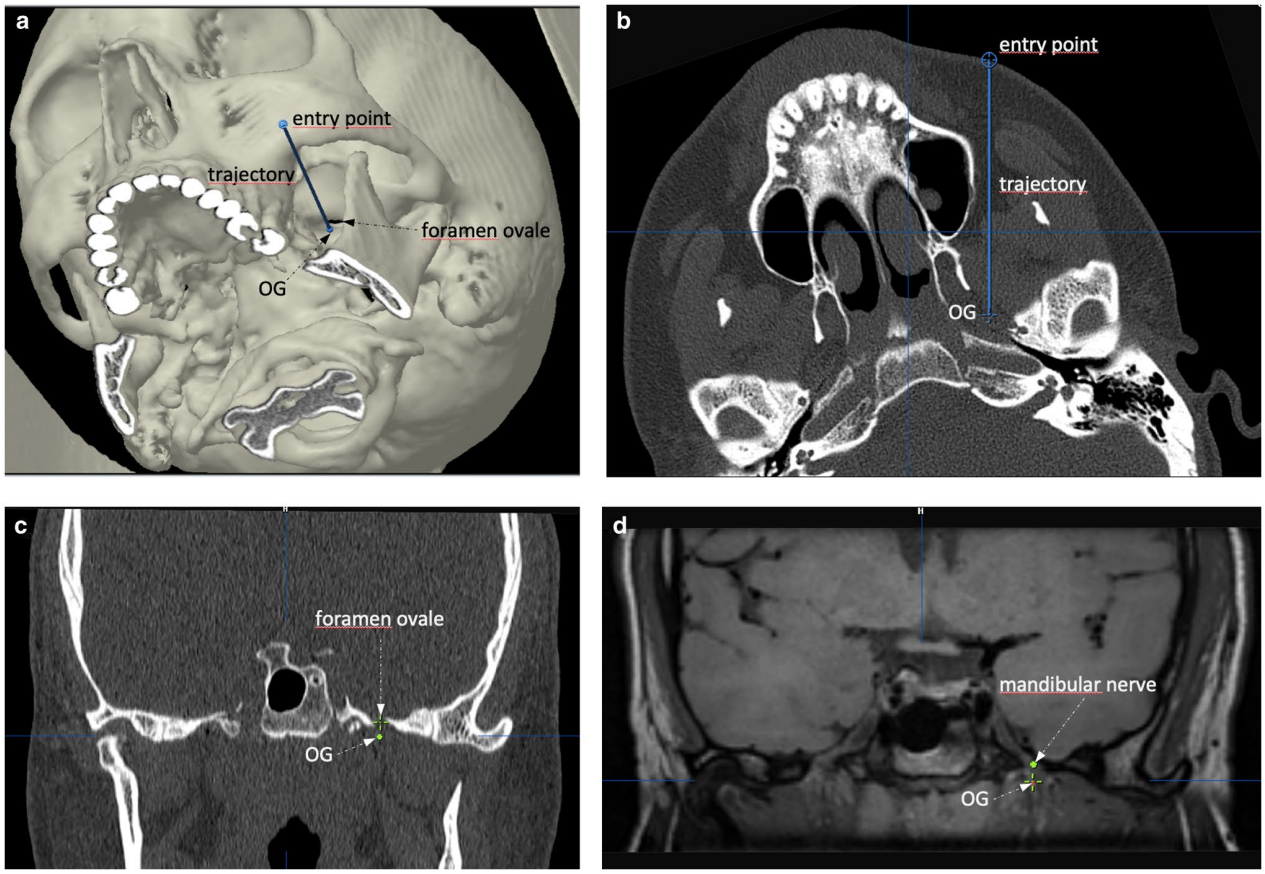

Fig. 3.—Example of the trajectory planning in patient number 6. (a) 3D reconstruction of the trajectory toward the left OG (antero-infero-lateral view). (b) modified axial plan (trajectory-plan) on a CT scan to show the trajectory from the entry point to the left OG situated in the infratemporal fossa. (c) coronal plane through the left foramen ovale (green cross) on CT-scan. The left OG (green dot) was localized 4.5 mm inferior to the inferior aspect of the foramen ovale. (d) T1 image taken with a 3-Tesla scanner; coronal plane. The green dot is situated over the left mandibular nerve exiting the foramen ovale. The left OG was localized directly medial to the mandibular nerve and 4.5 mm inferior to the foramen ovale. OG: otic ganglion.

The study protocol was approved by the regional ethical committee (REK 2016/2322). All participants provided written informed consent before participating in the study. The trial was registered in the EUDRACT database: 2016-004213-28 and at ClinicalTrials.gov (NCT03066635). The allocation of the study was not correctly stated in ClinicalTrials.gov (this study was not planned as a randomized trial). The trial was conducted in accordance with the original protocol.

SPSS version 25.0 (SPSS Inc, Chicago, IL, USA) was used in the data analyses. For efficacy measures we used the Wilcoxon signed-rank test, and 2-sided $P < .05$ was considered statistically significant. Results are given as median and range. Means (±SD) were also calculated only in order to produce comparable results to other studies targeting the SPG using the same device as this study[20] even though the assumptions required to use parametric descriptive statistics could not be verified.

Since this is an exploratory safety study, no power calculation was performed prior to start.

This study was conducted following GCP guidelines (Good Clinical Practice CPMP/ICH/135/95). The protocol for the study was elaborated following the Guidelines for controlled trials of drugs in CH of the International Headache Society with the exception that patients using antidepressants are not excluded. Patients with CH are severely affected by their condition and many use antidepressants. By not excluding those using antidepressants, the results of the study will have a higher generalizability and will be more relevant for this group of patients.

RESULTS

A total of 11 patients were screened. One patient was considered a screen failure during baseline (the patient had less than 4 attacks per week during the baseline period). Ten patients (5 women and 5 men, all white Caucasian) completed the study. See Table 1 for demographics of the sample.

Patients had tried a mean of 2.6 evidence-based prophylactic medications (minimum 2 of and maximum of 4) prior to inclusion in this trial. One patient was currently using lithium, 2 patients verapamil, and 1 patient melatonin. Six patients had previously tried suboccipital steroid injections, 6 patients had tried lithium, 8 patients had tried verapamil, and 2 patients had tried melatonin. All patients had tried oxygen but only 5 were using it as a current treatment. Eight patients were currently using sumatriptan and 2 patients had tried it before inclusion but were not using it because of lack of effect. No patients were currently using steroids under the study (patient number 9 started prednisolone 4 weeks after injection and was considered a protocol violator; see under "*Secondary outcomes*").

Patient number 9 was also considered a protocol violator since this patient started prednisolone 4 weeks after injection.

A total of 4 patients had previously tried treatment with subcutaneous BTA ipsilateral to their CH attacks using a "follow the pain" paradigm.

Primary Outcome (Safety).—For the primary outcome, data from all 10 patients were analyzed. There were a total of 17 AEs. Six out of 10 patients experienced AEs. The median number of AEs per patient was 1.0 (minimum 0-maximum 6). The mean number of AEs per patient was 1.7 (95% CI 0.2-3.2). SAEs were experienced by 0% of patients (95%CI: 0% to 30%; Table 2). In order to calculate the upper bound for SAEs, the statistical rule of 3 was used.[24] This methodology offers only an approximation and the real "true" upper bound of risk in such a small sample is difficult to estimate. All adverse events were considered to be mild. All AEs resolved within the 6-months follow-up. Three patients had to use analgesics due to pain in the injection site the day after the injection (paracetamol/acetaminophen in 2 patients and diclofenac in 1 patient). In these 3 patients, the pain at the injection side disappeared within 1 week. None of the patients had to use analgesics more than 2 days after the injection. One of the patients experienced problems to "articulate speech" during the first week after injection. This patient (patient number 6) did not have clinical dysarthria and symptoms were thought to be secondary to local discomfort after the injection. The same patient complained of discomfort when swallowing, but was able to swallow liquids and solids. This was also assumed to be secondary to local discomfort after the injection and disappeared at month 2. None of the

Table 2.—Adverse Events and Date of Resolution

Adverse Events	Number of Patients						
Resolved	<4 weeks	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Pain or swelling	3						
Jaw problems	1						
Chin numbness	2						
Hyperacusis							1
Tinnitus				1			
Ear fullness	1			1			
Dry mouth	1				1		1
Discomfort swallowing			1				
Articulation difficulties	1						
Nasal voice				1		1	

No AEs lasted beyond the follow-up of this study.

AEs required specific treatment. One of the 3 patients who reported dry mouth had diabetes and described that this might have been an issue before the injection. None of the 10 patients experienced AEs such as nasolabial fold asymmetry, diplopia or dry eye, which have been reported in pilot trials performing a block with BTA toward the SPG using the same device as in this study.[20-22] Patients reported pain in a numeric rating scale (NRS) from 0 to 10 immediately after the injection. The median pain after injection was 0.56 (range 0-3.5) and the median pain 1 day after injection was 0.7 (range 0-2). The AE profile in the 5 patients who received 25 IU of BTA was similar compared to those who received 12.5 IU of BTA (see Table 3).

The procedure was generally well tolerated with AEs being mild and transient. When asked 6 months after injection, 8 out of 10 patients in this study would recommend this treatment to other patients and 5 out of 10 patients would be interested in repeating the treatment. When asked about the satisfaction of the treatment, 4 patients answered "little," 2 "moderate," 2 "good," and 2 "very satisfied."

Secondary Outcomes (Efficacy).—For the secondary outcomes, we have analyzed data for 7 patients. Three patients had incomplete data and were excluded from the secondary outcome analysis. Patient numbers 3 and 5 were protocol violators since they did not record at least 80% of their headache diaries. Patient number 9 was also considered a protocol violator since this patient started prednisolone 4 weeks after injection.

One patient was a responder with at least 50% reduction of the number of attacks at month 2 compared to baseline (patient 4).

A Wilcoxon Signed Ranks Test, 2-sided, was performed to compare the number of attacks, attack

Table 3.—Dose of BTA Received, AEs, Median Number of Attacks at Baseline and Reduction in Attack Frequency at Month 2 Compared to Baseline

			Main Secondary Outcome (Attack Frequency per Week)	
Patient	Dose BTA (IU)	AEs	Baseline	Month 2
1	12.5	None	12.75	−23.5%
2	12.5	Pain (injection side) Chin numbness Dry mouth	7.75	−6.5%
3†	12.5	Pain (injection side) Jaw discomfort Hyperacusis Tinnitus Ear fullness Dry mouth	NA	NA
4	12.5	Dry mouth	15.00	−51.7%
5†	12.5	Pain (injection side) Chin numbness	NA	NA
6	25	Ear fullness Discomfort swallowing Articulation difficulties Nasal voice	19.50	+2.6%
7	25	None	25.75	−44.7%
8	25	Nasal voice	17.00	−1.5%
9†	25	None	NA	NA
10	25	None	18.25	−23.3%

AEs = adverse events; BTA = botulinum toxin type A; IU = international units; NA = not available.
†Patients number 3 and 5 were non-compliant with the headache diary and were considered protocol violators; patient number 9 started prednisolone 4 weeks after injection and was also considered a protocol violator.

Table 4.—Results

	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Median number of attacks per week (min-max)†	17.0 (7.8-25.8) 95% CI: 11.3-21.8	17.3 (6.0-23.5) $P = .499$	14.0 (7.3-20.0), $P = .051$ 95% CI: 8.3-17.2	14.3 (4.8-20.8) $P = .150$	14.5 (6.3-21.8) $P = .310$	12.8 (1.5-20.8) $P = .115$	13.0 (4-20.5) $P = .063$
Median attack duration (min-max)†	48.4 (37.3-135.4) 95% CI: 32.7-107.2	62.3 (21.3-143.5) $P = .866$	75.8 (31.4-170.3), $P = .063$ 95% CI: 41.4-143.7	95.5 (29.8-184.9) $P = .063$	95.5 (27.6-179.2) $P = .063$	61.7 (25.6-179.3) $P = .237$	90.0 (29.4-169.2) $P = .310$
Median intensity per attack (min-max)†	2.8 (1.5-4.0) 95% CI: 2.0-3.4	2.3 (1.2-4.0) $P = .176$	2.9 (1.6-4.0), $P = .237$ 95% CI: 2.2-3.5	3.0 (1.7-3.9) $P = .499$	3.0 (1.5-3.9) $P = .917$	2.8 (1.5-3.7) $P = .866$	2.8 (1.5-3.6) $P = .866$
Median days with attacks with autonomic symptoms (min-max)†	28.0 (6-28) 95% CI: 16.5-28.6	14.0 (1-28) $P = .028$	22.0 (0-28), $P = .058$ 95% CI: 9.2-27.3	19.0 (0-28) $P = .116$	18.0 (0-28) $P = .225$	16.0 (0-28) $P = .046$	21.0 (0-28) $P = .046$
Median triptan doses per month (min-max)†	29.0 (0-78) 95% CI: 4.9-54.8	16.0 (0-80) $P = .497$	4.0 (0-124), $P = 1.0$ 95% CI: −12.6-70.9	5.0 (0-122) $P = .600$	3.0 (0-135) $P = .865$	5.0 (0-122) $P = .600$	7.0 (0-88) $P = .249$
Median days without attacks (min-max)†	0.0 (0-8) 95% CI: −0.4-4.8	4.0 (0-13) $P = .141$	5.0 (0-11), $P = 1.0$ 95% CI: 0.1-7.9	5.0 (0-15) $P = .357$	4.0 (0-18) $P = .414$	10.0 (0-22) $P = .066$	4.0 (0-20) $P = .273$
Median number of attacks intensity 3 or 4 (min-max)†	34.0 (5-85) 95% CI: 11.5-67.1	15.0 (6-70) $P = .091$	30.0 (8-62), $P = .310$ 95% CI: 14.3-52.8	41.0 (9-72) $P = .866$	42.0 (5-87) $P = 1.000$	36.0 (1-44) $P = .397$	42.0 (3-67) $P = .352$
Median headache severity index (min-max)†,‡	7.0 (3.8-33.8) 95% CI: 3.2-23.6	8.2 (1.8-39.3) $P = .612$	13.6 (2.6-34.9), $P = 1.0$ 95% CI: 3.9-25.9	16.1 (2.4-26.2) $P = .866$	19.9 (2.4-23.7) $P = .735$	9.4 (0.5-22.3) $P = .499$	13.2 (1.4-25.2) $P = .612$
Median HIT-6 (min-max)§	66.0 (60-72) 95% CI: 62.7-68.3	64.0 (56-68), $P = .127$ 95% CI: 60.7-66.5	—	65 (57-76) $P = 1.0$	—	—	65 (58-76) $P = .181$
Median CAPS scale (min-max)¶	5 (2-9) 95% CI: 3.0-6.6	3.5 (1-9), $P = .071$ 95% CI: 2.3-5.7	—	—	—	—	5 (3-7) $P = .518$

P values are given at Month 2 (compared to baseline) where the main efficacy endpoint was measured; *P* values for HIT-6 and CAPS scale are given at Month 1, where these questionnaires were administered.

CH = cluster headache. HIT-6 = Headache Impact Test-6 score.

†Data for 7 patients. Patients 3, 5 and 9 were protocol violators and did not produce data that could be analyzed. Patients 3 and 5 filled less than 80% of the headache diary and patient 9 started prednisolone 1 month after injection.

‡Duration (min) × intensity × frequency/1000.

§Data for 9 patients. Two of the protocol violators (patients 3 and 5) did answer the HIT-6 questionnaire and their data is included in this analysis. Data from the other protocol violator (patient 9) is not included since this patient started prednisolone one month after injection.

¶Data for 10 patients with exception of "month 6" where one of the patients did not answer the questionnaire.

duration, maximal pain intensity, autonomic symptoms, use of triptans, use of oxygen, days without attacks, headache severity index at baseline, and at month 2 after injection (see Table 4). One of the 5 patients who used oxygen under the study was a protocol violator. The change in the use of oxygen before and after the study treatment of the 4 other patients was not statically significant.

The median number of attacks per week at baseline was 17.0 [7.8 to 25.8] vs 14.0 [7.3 to 20.0] in the 2nd month following injection; difference: 3 (95%CI: −0.3 to 7.9), $P = .063$. None of the other secondary efficacy measurements at Month 2 were statistically significant. Correction for multiplicity was not performed given the exploratory nature of the study and that there was not a statistically significant reduction of the number of attacks per week at month 2 after injection compared to baseline. Table 3 shows the mean reduction of the number of attacks at Month 2 compared to the baseline for each participant. Figure 4 shows the mean attack frequency per week over time.

A post hoc analysis comparing patients who received 12.5 IU of BTA and patients who received 25 IU of BTA toward the OG did not show any differences.

DISCUSSION

In this pilot study, we found that a block with BTA toward the OG using a new navigation tool (the MultiGuide) appears to be safe in this pilot study population. No serious AEs were reported in these 10 patients. Qualitative questionnaires showed that patients were most satisfied and experienced no or little pain after injection. The majority of patients would recommend this treatment to other patients and half of them would be interested in repeating the study treatment. Patients described AEs as mild and transient.

None of the secondary outcomes was statistically significant. A reduction of the median number of attacks per week was observed but this was not statistically significant. The median duration of the attacks was increased at follow-up in 6 of the patients (see Table 4), though this was not statistically significant. We cannot exclude that the study treatment might have increased the duration of the attacks, yet this observation might be due to the fluctuation of the disease in a small number of patients. There were no clinically relevant differences regarding AEs and the main secondary endpoint between the 5 patients who received 12.5 IU of BTA and the 5 patients who received 25 IU of BTA toward the OG.

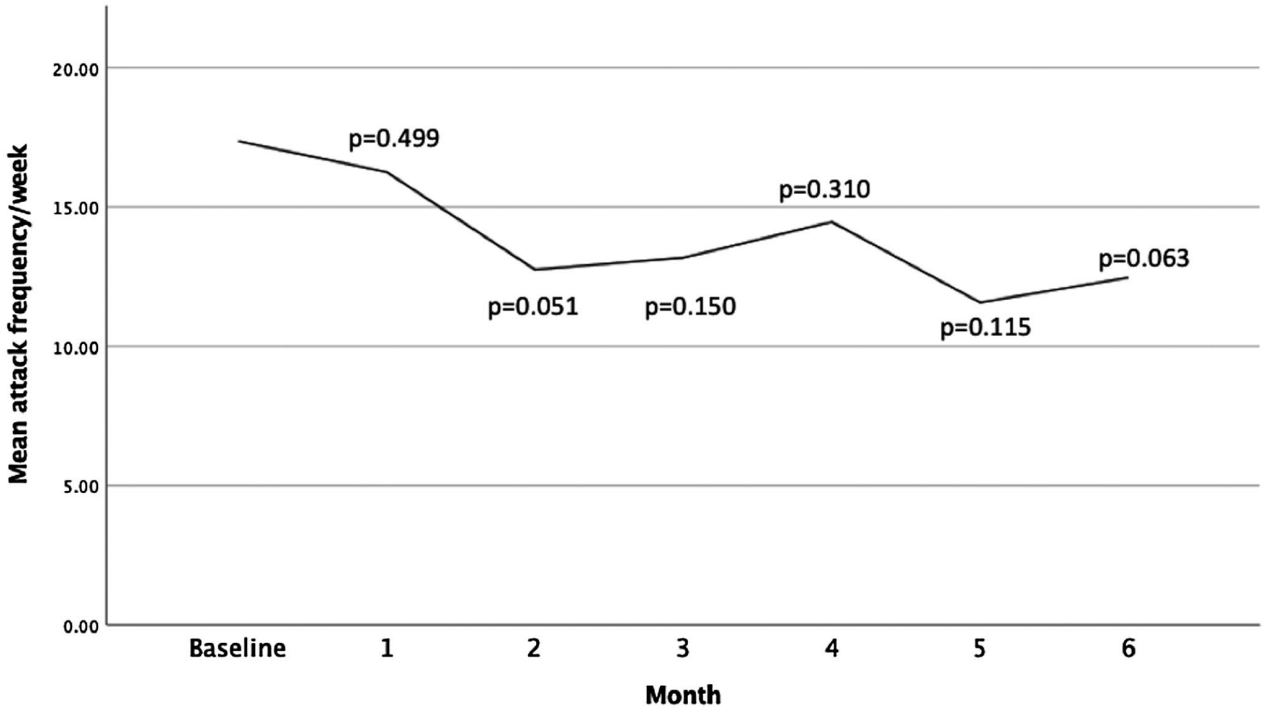

Fig. 4.—Mean attack frequency per week over time.

The OG was challenging to localize on 3Tesla MRI because of its small size. To the best of our knowledge, there are no studies that have depicted the OG in living humans on MRI. For this reason, we used 2 anatomical landmarks to localize the OG: the mandibular nerve and the foramen ovale. These 2 structures are easily identified on fused MRI and CT-scans. It has been described that the OG is consistently located immediately medial to the mandibular nerve[8] and its distance to the foramen ovale has also been documented.[1] Currently, there are no biomarkers to confirm target engagement with the OC and we can, therefore not exclude a lack of target engagement. To enable future studies targeting the OG, the first step may be to establish a reliable methodology to identify the OG in living humans, either by refining existing 3 Tesla MRI imaging protocols or possibly using newer techniques such as 7 Tesla MRI.

Several pharmacological substances have been used toward the SPG.[6] Once the feasibility to target the OG is established it will be important to evaluate whether substances such as local anesthetics or steroids can also be used toward this novel target.

Limitations of the Study.—This study did not have a control group and included a small number of patients. In such interventional studies, the placebo response could be high and regression to the mean and periods of remission may bias the results in uncontrolled studies.[25] All 10 patients were white Caucasians; the topography of the OG should be validated in a larger and more diverse sample. As noted, an indirect marker of the position of the OG was used, and we cannot be sure that the BTA reached the OG.

CONCLUSION

Injection of BTA toward the OG in patients with chronic CH appears to have an acceptable safety and tolerability profile. We did not observe a reduction of the median number of attacks per week at month 2 after injection compared to baseline (main secondary endpoint).

We cannot be certain that BTA reached the OG. Biomarkers to confirm target engagement with the OG and a better description of the OG's topography are needed in order to advance in understanding whether the OG could be a new target for the treatment of chronic CH and other trigeminal autonomic cephalalgias.

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