Doctoral theses at NTNU, 2021:98

Joan Crespi Vidal

# Cranial autonomic ganglia in headache disorders

## A small step towards a pain-free world

Doctoral thesis

**NTNU**
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Neuromedicine and Movement Science

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Trondheim, April 2021

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# 1 English summary

Headache disorders are amongst the most prevalent causes of disability worldwide. Most of the effort to develop new therapeutics has focused on migraine. Patients suffering from less common headache disorders such as trigeminal neuralgia (TN) or cluster headache (CH) are also in need of new and better treatments. Our group has developed a new navigation based surgical tool that allows accurate targeting of small anatomical structures that might be involved in cranial and facial pain. Two previous pilot trials have used this technique to inject botulinum toxin type A (BTA) towards the sphenopalatine ganglion (SPG) in 10 patients with intractable chronic CH (1) and in 10 patients with intractable chronic migraine (2). In this Thesis, we further explore the possibilities of this new device.

Most of the studies targeting the SPG do not localize the ganglion directly and use anatomical landmarks which have not been validated (3). Our group has depicted the SPG in living humans using MRI for the first time (4). Nonetheless, MRI might not always be available or some patients might have medical contraindications to undergo this examination. For this reason, we developed an algorithm to predict the location of the SPG using bony landmarks identified in CT-scans (paper 1).

Classical TN is not classified under trigeminal autonomic cephalalgias but recent studies have shown that one third of the patients might present autonomic symptoms and the SPG has been involved in its pathophysiology. In paper 2, we conducted a pilot study with 10 patients with classical TN (ICHD-3 beta criteria). Patients were injected with 25 units (U) BTA towards the ipsilateral SPG. The primary outcome was the occurrence of adverse events (AEs). The main efficacy outcome was the number of TN attacks at weeks 5-8 after injection compared to baseline.

CH is the most common trigeminal autonomic cephalalgia and it inflicts great suffering among patients. The SPG has been involved in its pathophysiology but no other cranial autonomic ganglia have been targeted in this condition. In paper 3 we describe the rational for the role

of the otic ganglion (OG) in autonomic cephalalgias. The OG is a smaller and less studied cranial autonomic ganglion. It cannot be seen in CT-scans or in conventional MR imaging. Its relation to the mandibular nerve has been described to be constant in the literature, with the OG being in direct contact to the medial surface of the third division of the trigeminal nerve (5). The mandibular nerve can be easily localized in MRI. In order to target one structure, which cannot be directly depicted, at least one other anatomical landmark is necessary in addition to the mandibular nerve. The foramen ovale (FO) can be seen clearly in CT-images. One anatomical-cadaveric study describes that the OG "lies immediately below the FO", however the distance between the FO and the OG was not reported in this study (5). In order to target the OG we measured the average distance between the FO and the OG in 21 high definition photographs of 21 infratemporal fossae from 18 cadavers (paper 3).

In a pilot study with 10 patients with intractable chronic CH (paper 4), 5 patients were injected with 12.5 U of BTA and 5 patients with 25 U of BTA towards the ipsilateral OG. The primary endpoint was the occurrence of AEs. The main efficacy outcome was the number of attacks in month 2 after injection compared to baseline.

Main findings of this Thesis:

- The SPG localization can be predicted on CT-images using 2 bony landmarks. Localizing the SPG on CT-images will be important for patients with contraindications to undergo an MRI (e.g. claustrophobia, MR-incompatible metallic foreign bodies or stimulators, etc.), when access to MRI is limited, and in those patients where repeated injections are needed.
- Injection of BTA towards the SPG in classical TN (ICHD-3 beta) appears to be safe. We did not find any indication for effect in reducing the number of TN attacks after injection of 25 U of BTA towards the SPG. A better understanding of the role of the SPG in TN is necessary.
- The OG appears to have a constant location, being situated 4.5 mm inferior of the FO and medial to the mandibular nerve. The FO is easily localized on CT-scans and may be an interesting anatomical landmark when trying to develop navigation-based therapies towards the OG.

- Injection of BTA towards the OG in CH appears to be feasible and safe. We did not find a clear indication for effect in reducing the number of CH attacks after injection of 25 U of BTA towards the OG. A better description of the topography of the OG in living humans should precede further clinical studies targeting this structure.

# 2 Norsk sammendrag

Norsk tittel: «Kranielle autonome nerveknuter og deres rolle i hodepinelidelser»

Hodepine er et av de vanligste problemene i verden. Mesteparten av utviklingen av nye terapier har fokusert på migrene. Pasienter som lider av mindre vanlige hodepinetyper som trigeminusnevralgi (TN) eller klasehodepine (KH) har behov for utvikling av nye behandlingsalternativer. Vår forskningsgruppe har utviklet et kirurgisk verktøy som bruker nevronavigasjon for presis behandling av små strukturer i ansiktet som kan være viktig for smerter. To tidligere pilotstudier har brukt denne teknikken for å injisere botulinum toksin (BTA) mot nerveknuten sfenopalatint ganglion (SPG) i 10 pasienter med intraktabel kronisk KH (1) og i 10 pasienter med intraktabel kronisk migrene (2). I denne avhandlingen ville vi undersøke videre muligheter med denne nye metoden.

De fleste studier som har hatt SPG som behandlingsmål, fremstiller ikke nerveknuten direkte, men bruker ikke-validerte metoder med anatomiske referansepunkter for å lokalisere knuten (3). Vår gruppe har fremstilt SPG i levende mennesker ved bruk av MR for første gang (4). MR er ikke alltid tilgjengelig og noen pasienter har kontraindikasjoner. På grunn av dette, har vi utviklet en algoritme for å beregne lokalisasjonen av SPG ved bruk av benete landemerker identifisert i CT bilder (artikkel 1).

Klassisk TN er ikke klassifisert under de såkalte trigeminale autonome kefalalgier. Imidlertid har nye studier vist at en tredjedel av pasientene har autonome symptomer og nerveknuten SPG har blitt involvert i patofysiologien. I artikkel 2 gjennomførte vi en pilotstudie med 10 pasienter med klassisk TN (ICHD-3 beta kriterier). Pasientene ble injisert med 25 enheter (E) BTA mot ipsilaterale SPG. Det primære endepunktet var forekomst av bivirkninger (AEs). Hoved effektivitetsutkom var antall anfall med TN i ukene 5-8 etter injeksjon sammenlignet med baselineperioden.

KH er den vanligste trigeminale autonome hodepinen og forårsaker stor lidelse hos pasientene. Det er gode holdepunkter for at SPG har en sentral rolle i patofysiologien til KH, men rollen til andre kranielle autonome nerveknuter er mindre studert. Artikkel 3 er et grunnarbeid for å kunne studere nerveknuten kalt ganglion oticum (OG) i autonome kefalalgier. OG er mindre enn SPG og er for liten til å detekteres på CT eller konvensjonelle MR bilder.

For å kunne indirekte lokalisere OG trenger man minst to anatomiske landemerker. Det er kjent at avstanden mellom OG til mandibularisnerven er konstant (OG ligger i direkte kontakt med den mediale overflate av nerven (5)). Mandibularisnerven er enkel å finne på MR-bilder. I artikkel 3 undersøkte jeg å bruke foramen ovale i tillegg til mandibularisnerven som landemerke. Foramen ovale (FO) er enkel å identifisere på CT-bilder. En anatomisk kartlegging på kadaver har beskrevet at OG «ligger direkte under FO», men avstanden mellom FO og OG ble ikke rapportert i denne studien (5). For å kunne beregne lokalisasjonen til OG valgte vi å måle den gjennomsnittlige avstanden mellom FO og OG i 21 høyoppløsningssbilder av 21 infratemporale fossaer fra 18 kadavre (artikkel 3).

I en pilotstudie med 10 pasienter med intraktabel kronisk KH (artikkel 4) ble 5 pasienter injisert med 12.5 E BTA og 5 pasienter med 25 E BTA mot den ipsilaterale OG. Det primære endepunktet var forekomst av bivirkninger. Hoved effektivitetsutkom var antall anfall i måned nummer 2 etter injeksjon sammenlignet med baseline.

Hovedfunn i denne avhandlingen er:

- Man kan predikere lokalisasjonen av SPG i CT-bilder ved bruk av 2 benete landemerker. Dermed kan man unngå MR undersøkelse der dette er kontraindisert eller ikke tilgjengelig.
- Injeksjon av BTA mot SPG ved TN ser ut til å være trygt. Vi fant ingen holdepunkter for at behandlingen reduserer antall TN attakker. En bedre forståelse av SPGs rolle i TN er nødvendig.

- OG har en konstant lokalisasjon 4.5 mm under FO og medialt for mandibularisnerven. FO er enkel å se i CT-bilder og virker å være et velegnet anatomisk landemerke for navigasjons-baserte terapier mot OG.
- Injeksjon av BTA mot OG ved KH er gjennomførbart og virker å være trygt. Vi påviste ingen reduksjon i hyppigheten av KH-anfall etter injeksjon med 25 E BTA mot OG. En bedre beskrivelse av topografien av OG i levende mennesker bør gjøres før videre forsøk med å blokkere denne strukturen.

# 3 Acknowledgements

Thanks to all the people who collaborated in this doctoral Thesis and who try to make this world a better place.

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Thanks to the patients who participated in our studies and whom we will try to continue to help.

*“The world would be a better place if everyone had a ukulele”*

Jake Shimabukuro

# 4 **Abbreviations**

| | |
|---|---|
| AEs | Adverse events |
| BTA | Botulinum toxin type A |
| CH | Cluster headache |
| CM | Chronic migraine |
| CT | Computerized tomography |
| FO | Foramen ovale |
| ICHD-3 | International Classification of Headache Disorders 3rd Edition |
| MRI | Magnetic resonance images |
| OG | Otic ganglion |
| RCT | Randomized controlled trial |
| S-point | A point on the sphenoidal bone which was defined in an axial plane at the level of the centre of the VC used as a landmark to calculate sSPG (Figure 3, paper 1) |
| SD | Standard deviation |
| SPG | Sphenopalatine ganglion |
| sSPG | Predicted position of the SPG measured from the sphenoidal bone (S-point) |
| vcSPG | Predicted position of the SPG measured from the VC |
| TACs | Trigeminal autonomic cephalalgias |
| TN | Trigeminal neuralgia |
| U | Units |
| VAS | Visual analogic scale |
| VC | Vidian canal |

# 5 List of Publications

The Thesis is based on the following papers:

1. Crespi J, Bratbak D, Dodick DW, Matharu M, Jamtoy KA, Tronvik E. Prediction of the sphenopalatine ganglion localization in computerized tomography images. Cephalalgia Reports. January 2019. doi:10.1177/2515816318824690

2. Crespi J, Bratbak D, Dodick DW, Matharu M, Jamtoy KA, Tronvik E. Pilot Study of Injection of OnabotulinumtoxinA Toward the Sphenopalatine Ganglion for the Treatment of Classical Trigeminal Neuralgia. Headache. 2019;59(8):1229-39.

3. Crespi J, Bratbak D, Dodick DW, Matharu M, Senger M, Angelov DN, et al. Anatomical landmarks for localizing the otic ganglion: A possible new treatment target for headache disorders. Cephalalgia Reports. 2019;2:1-7.

4. Crespi J, Bratbak D, Dodick DW, Matharu M, Solheim O, Gulati S, Berntsen EM, Tronvik E. Open-label, multi-dose, pilot safety study of injection of onabotulinumtoxinA towards the otic ganglion for the treatment of intractable chronic cluster headache. Headache. 2020 Jun 25. doi: 10.1111/head.13889. Epub ahead of print. PMID: 32583902.

# 6 General introduction

## 6.1 Headache as a global health problem

Headache is among the leading causes of disability worldwide (6, 7). Despite this fact, headache disorders are still underdiagnosed in many countries and have been neglected as a major public health problem (8). Most of the major therapeutic developments in the last decades have been for the treatment of migraine. Many patients suffering from less common types of headache such as trigeminal neuralgia (TN) and cluster headache (CH) are in need of better treatments with less side effects.

There have only been 5 placebo-controlled randomized clinical trials (RCT) in TN in the last 10 years (Table 1).

Table 1: Summary of placebo-controlled trials published between 2010 and 2020 in TN. N: number of patients included in the study; BTA: botulinum toxin type A; U: Units; sc: subcutaneously; iv: intravenous; VAS: visual analogic scale; RCT: randomized clinical trial. Data from (9-13).

| Author | Drug | N | Comment | Result | Year |
|---|---|---|---|---|---|
| **Wu CJ *et al*** | BTA sc | 40 | 75 U BTA or saline were injected sc following the pain. Primary endpoint: pain severity and attack frequency per day. Response to treatment was defined as a ≥50% decrease in pain score from baseline to endpoint. | 68.2% responders in the BTA group vs 15% in the placebo group. 66.7% patients could not guess whether they had received BTA. 11.9% guessed the wrong answer. BTA significantly reduced pain intensity at week 2 and pain attack frequency at week 1 (effect was sustained until week 12). | 2012 |
| **Zúñiga C *et al*** | BTA sc | 36 | 50 U BTA or saline were injected sc in the affected area. | Month 3 after injection: VAS 4.75 (BTA) vs 6.94 (placebo), p = 0.01. | 2013 |
| **Stavropoulou *et al*** | Lidocaine iv | 20 | Crossover design. Blinding was not assessed. | VAS reduction % pre-/posttreatment was 76.4 for lidocaine and 40.1 for placebo (p<0.001). | 2014 |
| **Zhang H *et al*** | BTA sc | 84 | 28 patients received placebo, 27 received 25 U BTA and 29 received 75 U BTA. Blinding not assessed. Four patients (2 from the placebo group, 1 from the 25 U group and 1 from the 75 U group) withdrew from the study due to lack of efficacy, leaving data on 80 patients for the final analysis. | VAS scores of the groups receiving 25 and 75 U significantly lower compared to placebo as early as week 1, and sustained until week 8. No significant difference in VAS between patients receiving 25 and 75 U. The response rates in the 25 U group (70.4%) and 75U group (86.2%) were significantly higher than in the placebo group (32.1%) at week 8, and there was no significant difference between 25 and 75 U groups. | 2014 |
| **Zakrzewska JM *et al*** | A Nav1.7 selective sodium channel blocker | 67 | Double-blind, multicentre, RCT withdrawal phase 2a trial. | Negative for primary endpoint (difference between groups in the number of patients classified as treatment failure during double blind phase). | 2017 |

In TN, carbamazepine is the drug with best evidence in the treatment of pain on the long term (14). The failure rate of this drug might be as high as half of the patients at 5 to 10 years (14). Oxcarbazepine might be as effective as carbamazepine (14, 15) with less adverse effects (16). Other drugs such as lamotrigine, gabapentin, pregabalin, fosphenytoin, and botulinum toxin have a lower degree of evidence (14). Most of the patients using these drugs experience side effects such as dizziness, drowsiness and nausea. Many of these patients or those not becoming pain-free will be offered surgical interventions, which also pose a risk for severe side effects (surgical interventions in TN are further described in section 6.2. of this Thesis).

Suboccipital steroid injection is the only treatment with level A evidence in the treatment of chronic CH (17, 18). In the last 10 years there have only been 7 placebo or sham controlled RCTs in chronic CH (Table 2).

Table 2: Summary of placebo-controlled trials published between 2010 and 2020 in chronic CH. N: number of patients in the study; cCH: chronic cluster headache; eCH: episodic CH; OR: odds ratio; CI: confidence interval; nVNS: non-invasive vasal nerve stimulation; DBS: deep brain stimulation; AEs: adverse events; ITT: intention to treat. Data from: (17, 19-26).

| Author | Therapy | N | Comment | Result | Year |
|---|---|---|---|---|---|
| **- Teva Pharm.** | Fremanezumab | 259 | Primary endpoint: mean change in monthly average number of CH attacks from weeks 0-12 | Study terminated (futility analysis revealed that the primary endpoint was unlikely to be met). | 2020 |
| **Dodick DW *et al*** | Galcanezumab | 237 | Randomized, placebo-controlled | Galcanezumab 300mg did not achieve its primary (overall mean change from baseline in weekly attack frequency) and key secondary endpoints (≥50% response rate and % of patients meeting sustained response). | 2020 |
| **Goadsby PJ *et al*** | SPG stimulation | 93 cCH | Randomized, sham-controlled, parallel group, double-blind. | The proportion of attacks for which pain relief was experienced at 15 min was 62.5% (95% CI 49.2-74.1) in the SPG stimulation group versus 38.9% (95% CI 28.6-50.3) in the control group (OR 2.6 [95% CI 1.3-5.3]; p=0.008). | 2019 |
| **Goadsby PJ *et al*** | nVNS ACT2 study | 102 CH 65 cCH | Primary efficacy endpoint: proportion of all treated attacks that achieved pain-free status within 15 minutes after treatment initiation. | nVNS and sham were not significantly different for the total cohort. In the eCH subgroup, nVNS (48%) was superior to sham (6%; p < 0.01). No significant differences between nVNS (5%) and sham (13%) were seen in the cCH subgroup. | 2018 |
| **Silberstein SD *et al*** | nVNS ACT1 study | 150 CH 48 cCH | Primary end point: response rate, i.e. proportion of subjects who achieved pain relief (pain intensity of 0 or 1) at 15 minutes after treatment initiation for the first CH attack without rescue medication use through 60 minutes. | ITT: 133 subjects, 60 nVNS-treated (eCH, n=38; cCH, n=22) and 73 sham-treated (eCH, n=47; cCH, n=26). Response was achieved in 26.7% of nVNS-treated subjects and 15.1% of sham-treated subjects (p=0.1). Response rates were significantly higher with nVNS than with sham for the eCH cohort (nVNS, 34.2%; sham, 10.6%; P=0.008) but not the cCH cohort (nVNS, 13.6%; sham, 23.1%; p=0.48). | 2016 |
| **Schoenen J *et al*** | SPG stimulation | 32 cCH | Primary efficacy endpoint: pain relief at 15 minutes following the start of stimulation | 28 completed the trial. Pain relief was achieved in 67.1% of treated attacks compared to 7.4% of sham-treated and 7.3% of subperception-treated attacks (p<0.0001). 19 of 28 (68%) patients experienced a clinically significant improvement: 7 (25%) | 2013 |

| | | | | | |
|---|---|---|---|---|---|
| | | | | achieved pain relief in ≥50% of treated attacks, 10 (36%), a ≥50% reduction in attack frequency, and 2 (7%), both. Industry sponsored. | |
| **Leroux E *et al*** | Suboccipital steroid injections | 43<br>15 cCH | Primary outcome: reduction of the number of daily attacks to a mean of ≤2 in the 72h period 2-4 days after the 3rd injection | 20 of 21 patients who received cortivazol had a mean of two or fewer daily attacks after injections compared with 12 of 22 controls (odds ratio 14·5, 95% CI 1·8-116·9; p=0·012). | 2011 |
| **Hakim SM *et al*** | Warfarin | 34 | Cross-over design. Primary outcome: occurrence of remission lasting ≥4 weeks. | ITT analysis: 17 patients (50%) underwent remission for ≥4 weeks in the warfarin group vs 4 patients (11.8%) in the placebo group (p=0.004) | 2011 |
| **Fontain D *et al*** | DBS | 11<br>cCH | prospective crossover, double-blind, multicentric. | Negative for primary endpoint (weekly attack frequency). 3 serious AEs. | 2010 |

CH has also been referred to as "suicide headache" and is known to inflict great pain in patients (27, 28). In a nationwide epidemiological study of CH in Norway we have found that, despite current treatment options, CH patients have an OR (adjusted for age and gender) of 3.9 (95% CI 2.6 – 5.8, p<0.0001) for suicide attempt ((29), submitted paper under review). Patients with CH also have a considerably increased risk for other medical and psychiatric comorbidities (see section 6.3). In one study by Zakrzewska *et al.* evaluating the impact of idiopathic TH, it was observed that up to 45% of patients had been absent from usual daily activities ≥15 days in the last 6 months (30). In the same study including 225 patients, 35.7% had mild-to-severe depression.

For all these reasons stated above, we believe that there is a need of new and better treatments both in CH and TN.

## 6.2 The SPG in headache disorders

Patients with trigeminal autonomic cephalalgias (TACs) frequently display cranial autonomic symptoms. CH is a typical example and patients often experience symptoms such as conjunctival injection, epiphora, ptosis, nasal congestion, rhinorrhoea, oedema of the eyelid, and miosis (31). In migraine, autonomic symptoms are also usual and have been less studied than in CH (32). In a series of 100 patients with chronic migraine, nasal congestion was observed in 20%, eyelid oedema in 39%, conjunctival injection in 44%, and lacrimation in 49% of the patients (33). In that series of patients, cranial autonomic symptoms were unilateral in 26.9% (32).

The SPG is believed to be involved in the pathophysiology of TACs (34) and has been a target for treatment of primary headache disorders for over a hundred years (35). Afferent input (preganglionic parasympathetic fibres) reach the SPG via the Vidian nerve. The efferent output of the SPG (postganglionic fibers) travel with branches of the fifth cranial nerve to innervate meningeal vessels as well as mucous membranes of several structures (lacrimal gland, palate, nose, uvula , tonsils, and pharynx) (34). Different drugs and several approaches have been used to attempt SPG-block in several headache disorders (1-3, 34).

A feedback loop between the dural blood vessels and the trigeminocervical complex has been described (36, 37). The output of this system can be activated both via descending modulatory influences from supraspinal and supratentorial structures (remarkably the hypothalamus) and via a reflex arc from activated trigeminal nociceptors in the trigeminal nucleus caudalis (37, 38). The activation of this loop can produce the release of vasoactive and inflammatory peptides in mucosal structures in the face but also in the dura and in cranial vasculature (38). The release of such vasoactive and inflammatory peptides is able to activate trigeminal afferents (38). We believe that an SPG-block will affect the output of this loop and the consequent activation of the trigeminal sensory system peripherally (37), as shown in Figure 1.

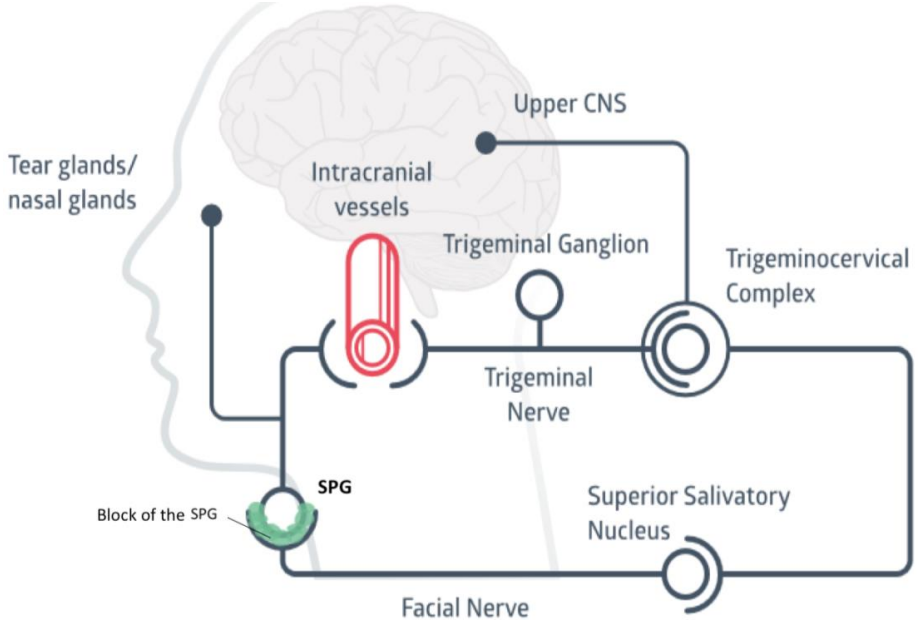


Figure 1: hypothesized mechanism for an SPG block. CNS: central nervous system; SPG: sphenopalatine ganglion. This illustration has been previously used in another publication by the author of this Thesis and permission has been obtained from the publisher (37).

## 6.1 Techniques to target the SPG: are we really getting there?

Most research groups targeting the SPG do not localize the ganglion directly but use indirect anatomical landmarks which have not been properly validated (3, 39). The different techniques used to attempt a block of the SPG have been reviewed by the author of this Thesis elsewhere (3).

*Intranasal application of local anaesthetics*

Local anaesthetics can be applied intranasally in order to attempt an SPG block (3). When local anaesthetics are applied intranasally, most of the volume will descend to the pharynx and the patient will often swallow the fluid, usually complaining of a bitter taste after the procedure (40). Thus, the final volume of local anaesthetics that remains on the surface of the

sphenopalatine foramen to passively diffuse to the SPG is likely to be small (3). The bitter taste of most local anaesthetics creates a challenge for blinding (3). This matter has not been correctly assessed and might constitute an important bias in several studies (3). One study randomised 40 patients with postdural puncture headache to treatment with lidocaine 4% or placebo using a cotton swab applied intranasally (41). In this positive study, blinding was assessed and shown to be correct (41).

An assumption by many authors has been that a local anaesthetic applied intranasally in the proximity of the sphenopalatine foramen can reach the SPG by free diffusion (3, 35, 42-45). This hypothesis would require that the distance between the SPG and the surface of the nasal mucosa is small enough (3). In a classical study, the first author to report a block of the SPG estimated the distance to be as short as 1 mm and this fact has been cited among many groups advocating the therapeutic effect of intranasal administration of local anaesthetics (3, 46). Though, the author also described that the SPG may be as far as 9 mm from the sphenopalatine foramen and that there is substantial variability between individuals (46). Neither the sample size, nor the demographics of the sample or the methodology used to assess the localization of the SPG were described in that study published in 1909 (3, 46). Significant individual differences were reported in another study analyzing the structure and topography of 70 SPGs (47). The author of this study found the SPG's size to be constant, between 3 and 5 mm. Nonetheless, the position of the SPG in relation to the sphenopalatine foramen, the anterior foramen of the Vidian canal, the palatine bone, and the maxillary nerve were not constant. In that study, the SPG was located 10 mm from the nasal mucosa membrane in 20 cadavers and at a distance of 3-4 mm in 35 cases. In this cadaveric study, the SPG was surrounded by fatty tissue, which might produce an extra barrier that a drug administered intranasally would have to cross in order to reach the parasympathetic ganglion. The SPG was located inside the Vidian canal in some preparations, which would make the SPG inaccessible to intranasal administration of local anesthetics (3, 47). The SPG was directly under the nasal mucosa membrane in only 21.4% of the ganglia (17 out of 70) (47). We have measured the distance between the nasal mucosa and the SPG in 20 living humans (40 sides) using MRI (3). In our study, the mean distance between the surface of the nasal mucosa and the centre of the SPG was 6.77 mm (SD 1.75; range 4.00 – 11.60), which is higher than the distance described in cadaveric studies. The shorter distances reported in cadaveric studies

might have been a result of dessication of post-mortem tissue or due to other mechanical factors when dissecting the SPG (e.g. in order to present and visualize the SPG).

Besides the distance between the SPG and the surface of the nasal mucosa, there are other anatomical obstacles that local anaesthetics would have to overcome in order to reach this parasympathetic ganglion (3). These obstacles include the nasal mucosa, neurovascular structures (the sphenopalatine artery and vein, and the nasal branches of the maxillary nerve), and connective tissue filling the sphenopalatine foramen and adipose tissue in the sphenopalatine fossa between the SPG and the sphenopalatine foramen (Figure 2). The sphenopalatine foramen is not an open foramen and thus there is not a direct communication between the intranasal cavity and the sphenopalatine fossa, as depicted in Figure 3.

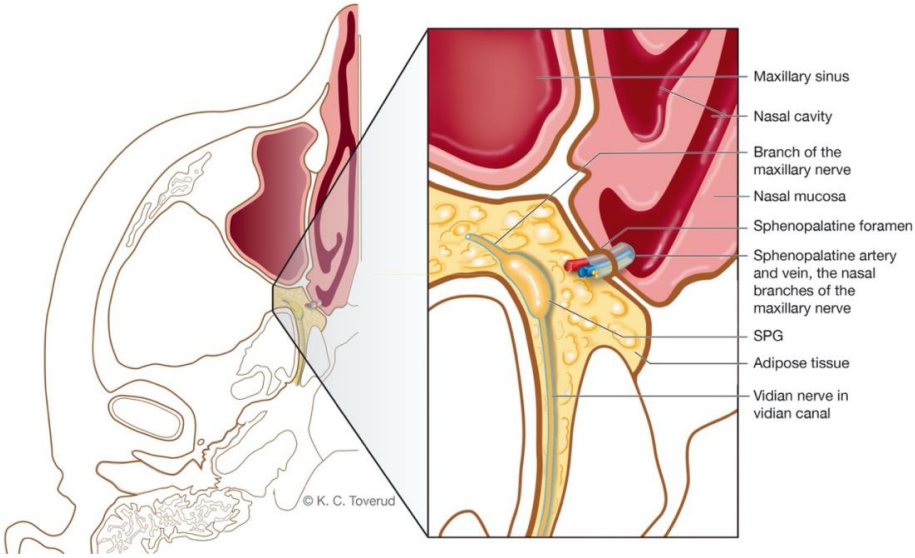


Figure 2: relationship between the sphenopalatine fossa and the nasal cavity. Any substance delivered intranasally over the sphenopalatine foramen would have to overcome the following barriers: the nasal mucosa, the sphenopalatine foramen, and fat tissue in the sphenopalatine fossa. SPG: sphenopalatine ganglion. This illustration was drawn by K.C. Toverud based on a sketch of the author of this Thesis and has been previously used in another publication by the author of this Thesis (3) with permission from the publisher.

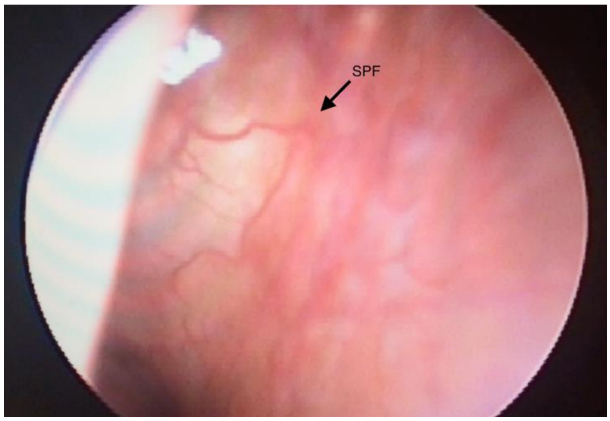


Figure 3: Rhinoscopy showing the mucosa of the author of this Thesis with the sphenopalatine artery (arrow) crossing the sphenopalatine foramen (SPF). One can observe that the nasal cavity and the sphenopalatine fossa are not connected via an open foramen. Mucosa covers the SPF, which contains connective tissue, and the sphenopalatine artery and vein. This figure has been previously used in another publication by the author of this Thesis (3); permission has been obtained from the publisher. We would like to thank Prof. Wenche Moe Thorensen for the acquisition of this photography.

*Invasive techniques targeting the SPG*

The SPG has been removed surgically and histologically verified in one study in patients with CH (48). The rest of the techniques that have targeted the SPG have not verified target engagement and the SPG has not been directly visualized, with the exception of 2 pilot studies presented below (1, 2) and the pilot study presented in paper 2 of this Thesis.

Neuromodulatory techniques have been used towards the SPG. In the methodological study describing the technique to implant an SPG-stimulator (49) the authors describe that the putative location of the SPG is "typically located posterior to the middle nasal turbinate, between the Vidian canal and the foramen rotundum". This presumed SPG localization has not been validated in vivo (39). Groups using pulsed radiofrequency or radiofrequency thermoablation have used fluoroscopy or CT-guided techniques, which cannot visualize the SPG (39, 50-61). Some studies that have injected alcohol towards the SPG have not used any

techniques for localization (62-64) while others have used fluoroscopy or CT-guided injections (39, 65-67).

We believe that the SPG is not likely to be blocked when it is targeted without previously localizing it, when old unvalidated anatomical landmarks are used or when drugs are applied intranasally (3, 39). Bratbak *et al.* has depicted the SPG in living humans on MRI for the first time (4). The same group has published 2 pilot trials where the SPG was localized using MRI (1, 2). MRI images fused with CT images were used to preplan the trajectory to target the SPG using a novel image guided technique. The same method to localize the SPG was used in the study presented in paper 2. When one intends to block the SPG using pharmacological substances or implant a stimulator towards the SPG, if direct visualization of the SPG (using MRI) is not accessible, reliable and validated landmarks to predict the position of this ganglion are needed.

*The MultiGuide: a navigation tool to target structures involved in headache disorders*

Our research group has developed a surgical device using image-guided navigation that allows clinicians to target small structures that might be involved in headache conditions. This tool, named the MultiGuide (Figure 1 in paper 2), has been used in a pilot trial in 10 patients with intractable chronic CH (1) and in another pilot trial in 10 patients with intractable chronic migraine (2). Both pilot trials found that injection of BTA towards the SPG using this minimally invasive technique appears to be safe.

Our group is currently using this device in several ongoing trials: a multicentre international placebo-controlled trial injecting 25 U BTA or placebo towards the SPG in patients with intractable chronic CH (ClinicalTrials.gov Identifier: NCT03944876), a placebo-controlled trial in treatment-refractory chronic migraine (ClinicalTrials.gov Identifier: NCT04069897) and in a randomized, double-blind, cross-over, placebo-controlled pilot study injecting BTA towards the SPG in patients with persistent idiopathic facial pain (ClinicalTrials.gov Identifier: NCT03462290).

In this Thesis we aim to explore whether injections of BTA towards the SPG using the MultiGuide are feasible and safe in other headache disorders such as classical TN (ICHD-3 beta) and whether another structure, the OG, could be a target of interest in chronic CH.

### 6.2 Trigeminal neuralgia

TN, formerly called "tic douloureux" (ICD-10 code G50.0,) was diagnosed in 5,448 patients in Norway between 2008 and 2016 (data from a Nationwide epidemiological study by the author of this Thesis (29)). According to the last International Classification of Headache Disorders (ICHD-3), classical TN is defined as recurrent paroxysms of unilateral facial pain (68). The pathophysiological mechanisms producing pain in classical TN have not been entirely clarified, but a neurovascular contact seems to be important (69). However, in one study, 78% of the patients had neurovascular contact on the asymptomatic side (69). A severe neurovascular contact (neurovascular contact with morphological changes, according to ICHD-3 terminology) was also seen in 13% of patients on the asymptomatic side in the same study. Animal models and clinical data suggest the participation of central pain mechanisms in TN (70, 71). The refractory period observed in classical TN points as well towards a role of the central nervous system in this condition (70, 72). If on induces a chemical lesion in the spinal trigeminal nucleus of cats or rats (with strychnine, alumina gel, penicillin or picrotoxin), spontaneous paroxysms of pain and a pronounced overreaction to tactile stimulation of the face will be observed (70). This paroxysms of pain and overreactivity to tactile stimuli is not observed when the same chemical lesion is directed towards the Gasserian ganglion, suggesting that this phenomenology has a central origin (70). Thus, there is likely more to classical TN than only a neurovascular contact and other anatomical structures might be interesting therapeutic targets in this condition.

The work presented in this Thesis has been produced under the transition between ICHD-3 beta and ICHD-3 criteria. A discussion on the terminology used in these two classifications is presented in section 8.2 ("Methods", paper 2). Where indicated, we have stated whether ICHD-3 beta or ICHD-3 criteria were used.

### 6.2.1 The SPG in TN

Maarbjerg *et al.* showed that 31% of patients with classical TN had autonomic symptoms in a prospective series of 158 patients (73) (a modified version of the ICHD-2 criteria was used in order to allow for sensory abnormalities). The list of symptoms observed in these patients comprised: tearing/conjunctival injection, running/clogged nose, increased sweating, and miosis/ptosis (73). Activation of the cranial parasympathetic output from the SPG might be responsible for these symptoms (34, 74, 75).

Pain sensitization is a complex process that might involve the SPG (76). Parasympathetic output might induce pain by sensitizing or activating central nociceptors (76). An SPG block could theoretically reduce the parasympathetic output and reduce the sensitization/activation of central nociceptive neurons and central nociceptors at the level of the spinal trigeminal nucleus (75).

As discussed further in section 10.2 of this Thesis ("Role of the SPG in TN" under "General discussion"), concomitant persistent pain appears to be common in patients with TN. This semiological aspect of TN is important in order to understand central facilitation of trigeminal nociceptive processing (71). Concomitant persistent pain was introduced as a clinical subtype of TN in the last ICHD criteria (68) after the description of the prevalence of this symptom by Maarbjerg *et al.* (77).

Even though ICHD-3 criteria have made it easier to identify patients with classical TN, including the demonstration on MRI or during surgery of a neurovascular compression (not simply contact), with morphological changes (typically atrophy or displacement) in the trigeminal nerve root, the diagnosis of TN remains mainly clinical. This is also true for TACs, where there are no useful biomarkers in clinical practice. The most important tool a neurologist must rely on is a good anamnesis. Even if some patients with TN might display autonomic symptoms, these are much more pronounced in TACs. The possibility of a "continuum of disease" between TN and TACs has been discussed (78). The concept "Tics in TACs" has been described (79, 80) ("tics" referring to the term for TN "tic douloureux"). The fact that differential diagnosis in patients with TACs and facial pain is still challenging (29, 81) might be the

underlying cause for such nosological discussions. If such a hypothesis of a “continuum of disease” were proved to be true, it would reinforce the idea that the SPG might play a role in some patients with TN and that the SPG constitutes an interesting target in this condition. From a broad biological perspective, it could be plausible that a group of diseases, which present with pain in the same part of the body, differing by how long the attacks last, share pathophysiological similarities so that there could be a “pathophysiological continuum”. Nonetheless, we believe that classical TN (ICHD-3 criteria) constitutes a separate entity than those diseases categorized under TACs. One should also consider that the observed autonomic symptoms in TN might be secondary to the pain condition (82) and not imply a primary involvement of the autonomic system.

Treatment options of TN comprise medical drugs and surgical interventions (83). High quality RCTs examining the role of the SPG in TN are lacking and the SPG’s role in TN has not been sufficiently established (75). Table 3 summarizes the studies that have attempted to block the SPG in TN.

Table 3: Summary of studies that have targeted the SPG in TN (modified and updated from Piagkou M et al. (84)). N: number of patients included in the study; CBZ: carbamazepine; GLOA: local ganglionic opioid analgesia at the superior cervical ganglion or sphenopalatine ganglion; VAS: visual analogic scale; CM: chronic migraine. Data from (65, 84-90).

| Author | N | Comment | Results | Year |
|---|---|---|---|---|
| **Manahan *et al.*** | 1 | The authors describe that the patient received a SPG block using bupivacaine 0.5% | The patient remained pain free as of 30 months after initial treatment. | 1996 |
| **Spacek *et al.*** | 39 | Retrospective analysis of 39 patients (1993-1994):<br>Group A (n=17): CBZ and acupuncture therapy;<br>Group B (n=11) CBZ and GLOA + acupuncture;<br>Group C (n=11): CBZ and GLOA without acupuncture | Number of patients who remained pain-free:<br>Group A: 8<br>Group B: 5<br>Group C: 2 | 1998 |
| **Grégoire *et al.*** | 1 | 3 separate CT-guided injections towards the SPG over 2 years | The authors describe that the patient became pain-free | 2002 |
| **Kanai *et al.*** | 25 | RCT, double-blind, placebo-controlled, crossover study. Intranasal lidocaine 8% spray | VAS reduction of more than 2cm in 14 patients of the lidocaine group and in 3 controls ($p<0.01$). Degree of blinding was not assessed. | 2006 |
| **Candido *et al.*** | 1 TN | Intranasal catheter Tx360® | The patient reported pain relief within the first 15 min. post-treatment. | 2013 |

Ho *et al.* have described that the grade of recommendation for SPG block in TN is grade B (91). Kanai *et al.* have conducted the only RCT in TN attempting to block the SPG (88). In this study, 25 patients were randomized to treatment with intranasal spray containing lidocaine (8%) or placebo for second-division TN in a cross-over fashion. Most patients in the lidocaine group experienced "prompt but temporary analgesia" (88). None of the studies described in Table 3 confirmed that the SPG was blocked (i.e. no biomarkers were provided). Intranasal administration of drugs has not been confirmed to produce an SPG block and proper blinding was not assessed in the RCT by Kanai *et al.* (3, 75).

Those patients with classical or idiopathic TN (ICHD-3 criteria) who do not have a positive effect of medical treatment, and those who do not tolerate or have unacceptable side effects are likely to be offered surgery (14, 75). A Cochrane review found that the quality evidence for efficacy of most surgical treatments for TN was low or very low because of the poor quality

of the studies (92). The incidence of TN raises with age (93). For this reason, many patients who might be referred to surgery are elderly and have a higher risk of potentially severe side effects after surgical procedures. The effectiveness of several surgical treatments in TN has been reported to be very high (75), but the number of patients included and the follow up tends to be short (92). Table 4 shows the prevalence of side effects observed in different TN treatment studies using microvascular decompression or percutaneous techniques.

Table 4: Complications in patients with TN undergoing microvascular decompression and different percutaneous therapies, based on a review Taha *et al.* in 1996 (94, 95).

| **Technique** | **Microvascular decompression [1*]** | **Glycerin-rhizotomy [2*]** | **Balloon-compression [2*]** | **Thermo-coagulation [2*]** | **Partial rhizotomy [3*]** |
|---|---|---|---|---|---|
| **Cases** | 1417 | 1217 | 759 | 6705 | 250 |
| **Perioperative morbidity** | 10% | 1% | 1,7% | 0,6–1,2% | 10% |
| **Perioperative mortality** | 0,6% | 0% | 0% | 0% | 0,6% |
| **Hypo-/dysesthesias** | 2% | 60% | 72% | 98% | 100% |
| **Mild dysesthesias** | 0,2% | 11% | 14% | 9–14% | 5% |
| **Severe dysesthesias** | 0,3% | 5% | 5% | 2–10% | 5% |
| **Anesthesia dolorosa** | 0% | 1,8% | 0,1% | 0,2–1,5% | 1% |
| **Anesthesia of the cornea** | 0,05% | 3,7% | 1,5% | 3–7% | 3% |

[1*] Microvascular decompression of the cerebellar superior artery; [2*] Trigeminal ganglion; [3*] Trigeminal nerve.

A review of percutaneous neuroablative treatments for TN published in 2014 found complication rates similar to the series presented in Table 4 (96). A review examining the effects of Gamma Knife treatment in TN found that between 11-80% of the patients develop hypesthesia in the trigeminal region (97). The risk of anaesthesia dolorosa, anaesthesia of the cornea and risk of hypoesthesia are the highest concerns of percutaneous techniques used in

TN (75). These surgical side effects tent to be permanent, but the effect of the treatment in most of the patients is not.

Neither RCTs comparing microvascular decompression versus neuroablative treatments nor RCTs comparing different neuroablative treatments in classical or idiopathic TN have been performed (14). For those patients with classical TN (ICHD-3 criteria) microvascular decompression might be preferred over gamma knife surgery or other neuroablative options (low quality evidence) (14). For those patients without a significant nerve compression (idiopathic TN according to ICHD-3 criteria), neuroablative treatments should be preferred (14). We are not aware of any sham-controlled surgical studies in TN. Most surgical sham-controlled studies will have inherent ethical challenges but if those challenges are properly managed, it would be of extreme importance in a condition (TN) were most surgical approaches have low or very low level of evidence.

The possibility of severe and permanent AEs in a considerable proportion of patients with TN who undergo surgery emphasizes the need for well tolerated, and minimally invasive treatments (75).

### 6.3 CH and the otic ganglion

CH causes great suffering to patients (27, 28). Most of the patients have episodic CH, but about 10-15% have chronic CH (68). The therapeutic options for this condition are limited and many patients do not respond to treatment or experience adverse events (98). The level of evidence for most current treatment options is scarce (18). Several studies have assessed the prevalence of CH but these studies have used different methodologies and the number of high-quality population-based studies is limited. Few studies have examined the incidence of CH. CH's lifetime prevalence is thought to be around 0.2-0.3% (99). The methodology of some studies has been criticized and need for larger population samples has been emphasized (100). A higher prevalence in men is constant in the literature, with a gender (M:F) ratio of about 3:1 (101, 102). In a Nationwide study of CH in Norway, we have found that the prevalence of CH was 48.6 per 100,000, and the male-to-female ratio was 1.47 (29). The estimated incidence of CH in our study was 3.0 per 100,000/year (29).

CH's comorbidity remains also insufficiently documented (103). The most common medical comorbidity appears to be migraine (29). The most common non-headache medical comorbidity in the same study was hypertension and the most common psychiatric comorbidity was depression (29). Suicidality is also a major problem in CH patients (29, 103-106). A history of substance abuse is a constant finding in the literature (29, 105, 107-109). Patients with CH have a higher risk of potentially severe medical and psychiatric comorbidities and higher use of opioid analgesics (29). This places this patient population at substantial risk of serious adverse health outcomes, beyond the disability caused by the headache disorder. Our nationwide study (29) emphasizes the need to systematically and comprehensively evaluate these patients from a general medical and psychiatric perspective in addition to a neurological evaluation. There is a risk that some or many of these diseases may be overlooked or not carefully investigated because of the very severe and highly disabling nature of the headache disorder itself.

### 6.3.1 The OG and its possible role in TACs

There are 3 major cranial parasympathetic ganglia other than the SPG: the ciliary ganglion, the OG and the submandibular ganglion (5, 37). The ciliary ganglion controls the contraction of the pupillary sphincter. The submandibular ganglion innervates the submandibular gland. Consequently, the ciliary and the submandibular ganglions are not likely to be involved in the pathophysiology of headache disorders. In contrast to the SPG, the OG has received less attention from neurologists, and previous to our study presented in paper 4 there have not been any attempts to target this ganglion for the treatment of headache disorders (5, 37). Frey's syndrome typically develops months after an injury of a branch of the mandibular nerve (82). It is produced by a lesion of the postganglionic fibres from the OG, leading to aberrant re-innervation and results in flushing and sweating of the cheek following exposure to gustatory stimuli (82). Common causes for Frey's syndrome are sharp injuries to the ganglion due to surgery or trauma (82).

The OG lies deep in the infratemporal fossa and its size is about 4mm long, 3 mm wide and 1.5 mm thick (110) (Figure 4). The OG's topography and syntopi (relationship to near structures) in humans has been described thoroughly in a cadaver study carried out in 21 halves of 18 human heads (5).

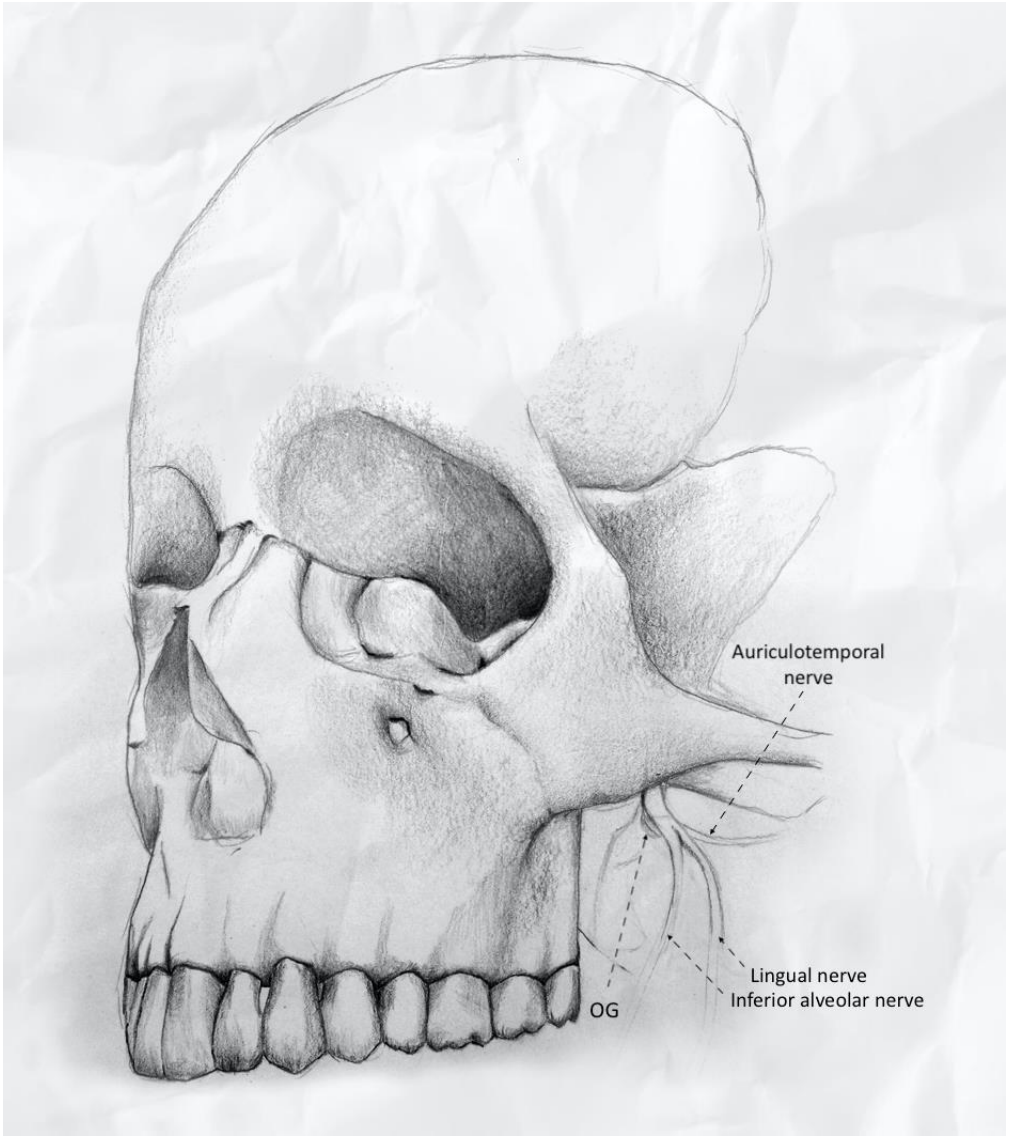


Figure 4: Anterolateral view showing the OG in the infratemporal fossa directly medial to the mandibular nerve after exiting the foramen ovale, just before its division into the inferior alveolar nerve and the lingual nerve. A modified version of this illustration, drawn by Gry E. Pedersen based on a sketch drafted by the author of this Thesis appears in paper 3 (37).

The OG is a small but complex structure. The most important adjacent structures, afferent inputs and efferent outputs are shown in Figure 5. From the inferior salivatory nucleus, the glossopharyngeal nerve carries preganglionic parasympathetic fibres (5). The IX$^{th}$ cranial nerve

exits the skull through the jugular foramen and then this fibres travel through the tympanic nerve and the lesser petrosal nerve to reach the OG in the ipsilateral infratemporal fossa (5). Postganglionic fibres projecting toward ganglia of the cavernous sinus and toward the trigeminal ganglion exit the OG with the external sphenoidal nerve (also called ramus communicans cum sinus cavernosus) (5)(Figure 5).

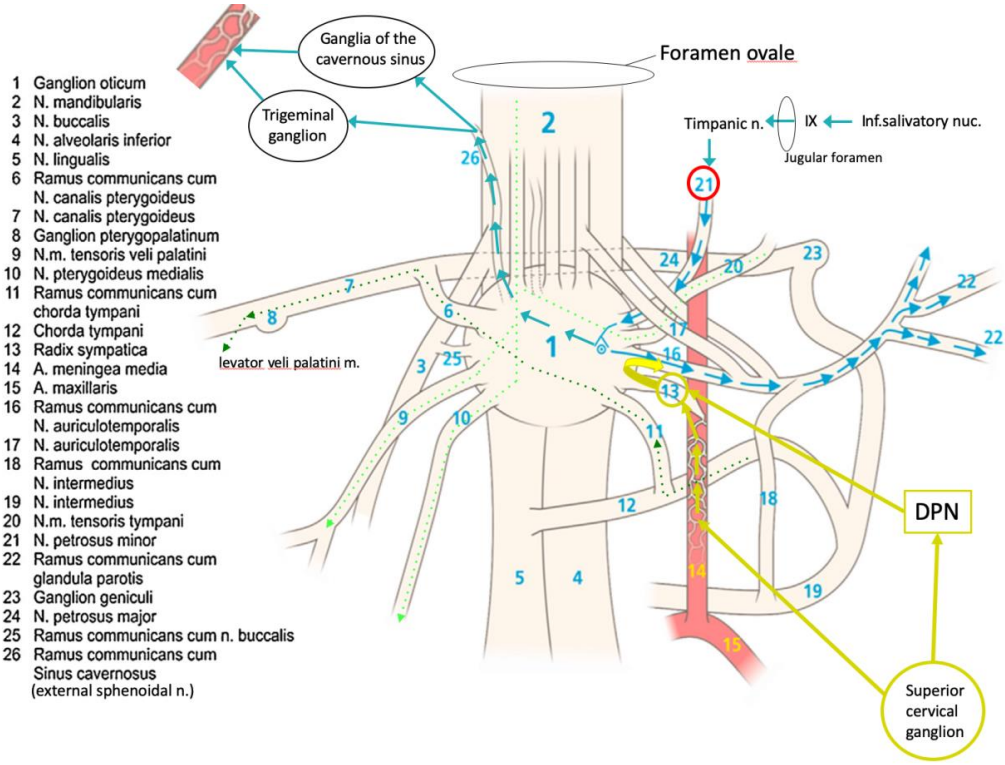


Figure 5: modified illustration of the left otic ganglion (nr. 1), observed from a medial view, with its most relevant near structures, afferent inputs and efferent outputs. The OG is situated medial to the mandibular nerve (nr. 2), superior to its bifurcation were the inferior alveolaris nerve (nr. 4) and the lingual nerve (nr. 5) originate (5). The buccal nerve is a sensory nerve (nr. 3). The parasympathetic fibers that reach the OG originate in the inferior salivary nucleus and travel along the IX$^{th}$ cranial nerve, the timpanic nerve, the lesser petrosal nerve (nr. 21) and then reach and synapse in the OG. This parasympathetic fibers continue then along with the auriculotemporal nerve towards the parotid gland. The sympathetic fibers originate in the superior cervical ganglion and travel through the plexus of the middle meningeal artery (nr. 14) and the deep petrosal nerve (DPN). This sympathetic fibers do not synapse in the OG. Sensory fibers from the third branch of the trigeminal nerve cross the OG without synapsing in it (light green discontinuous line). Some of these trigeminal sensory fibers travel towards the medial pterygoid nerve (nr. 10), innervating the medial pterygoid muscle. Others sensory

fibers travel towards the tensor muscle of the velum palatinum and the tensor tympani. Sensory fibres travel also from the IX$^{th}$ cranial nerve via the tympanic plexus and the lesser superficial petrosal nerve (nr. 21). Sensory and parasympathetic fibers travel from the OG to the trigeminal ganglion and ganglia of the cavernous sinus through the external sphenoidal nerve (also called ramus communicans cum sinus cavernosus, nr. 26). This connection from the OG towards intracranial neurovascular structures has been shown in different animal studies: in cats (111), rats (112, 113) and in monkeys (114). Suzuki *et al.* have also described parasympathetic and sensory innervation from the OG and the SPG in man (115). Motor fibers cross also the OG without synapsing (dark green discontinuous line). These motor fibers come from the facial nerve through the chorda tympany, cross the OG towards the ramus communicans cum nervus canalis pterygoideus (nr. 6) towards the levator veli palatine muscle. Modified with permission of Senger *et al.* (5).

*Role of the OG in salivation*

Parasympathetic fibers from the OG travel through the auriculotemporal nerve and innervate the parotid gland. Patients with CH might experience "increased and thickened saliva" (116) but this is not a constant, well documented semiological feature in CH. Few attempts have been done to measure salivation in CH. Measuring salivary production is challenging in healthy individuals (117), but more so in patients undergoing CH attacks.

Saunte C. measured saliva production in 14 patients with CH under basal conditions, during CH attacks and after stimulation with pilocarpine (116). Under basal conditions, salivation was of the same magnitude as in a control group of 20 students. This author managed to measure salivation during 8 CH attacks, but measurable quantities of saliva were obtained in only three cases. Unfortunately, these 3 cases had only wat he described as "weak pain attacks" and viscometry of the saliva could not be performed in any of the patients. In his paper, Saunte describes that these 3 patients felt that their mouths were dry under the CH attacks. After pilocarpine test, no difference was found between the symptomatic side and the asymptomatic side in CH patients and between CH patients and controls. In his paper from 1984, Saunte discusses that "the minimal salivation during attacks may strengthen the view (118) that a sympathetic stimulatory effect is exerted on the salivary glands during attacks" (116).

Nociceptive stimuli towards the eyes, nose, mouth or facial skin can trigger parasympathetic reflexes which might result in vasodilation, lacrimation, rhinorrhoea and salivation (82).

*Role of the OG in cerebrovascular regulation*

In a paper published in 1984, Goadsby PJ *et al.* showed that the OG is involved in the cranial vasomotor response in cats together with the SPG (119). Previous to this work, it was known that direct stimulation to the trigeminal nerve or to the facial nerve could trigger vasodilation of pial vessels, but whether and which cranial autonomic ganglia were involved had not been properly studied. For this reason, 27 cats were subjected to a C1/2 spinal cord section in order to eliminate peripheral effects of locus coeruleus stimulation (119). Then, blood pressure, common carotid flow, and common carotid resistance were assessed in different experimental conditions: 1. Both SPG and OG were intact; 2. Ipsilateral SPG dissected; 3. Ipsilateral OG dissected; 4. Both ipsilateral and OG dissected; 5. Contralateral SPG dissected; 6. Both SPG dissected. Following stimulation of the locus coeruleus, an increase in ipsilateral common carotid flow was observed. When the ipsilateral SPG or OG was removed, the facial dilator response was halved (119). The authors found a similar effect of the SPG and the OG in this reflex and describe that the dilator response is entirely mediated via these ganglia. The large part of the response mediated by the OG was surprising for the authors (119).
As discussed above, Walters. *et al.* also found cerebrovascular projections from the SPG and the OG to the middle cerebral artery in the cat using axonal tracing techniques (111). Further work studying the cranial parasympathetic pathway to the cerebral vessels has focused mostly on the SPG (120). It appears that this pathway arising in the superior salivatory nucleus in the pons can be activated by direct stimulation or via connections with other central neural vasoactive nuclei to increase cerebral blood flow independent to hypercapnia, hypoxia or autoregulatory responses (120).

Cholinergic fibers in the OG have been documented (120)(Figure 6) and the study of noncholinergic neuromessengers and neuropeptide receptors in the OG has also been examined (121). Vasoactive intestinal peptide (VIP), NOS- and PACAP-containing cell bodies are common in the OG (121). Nonetheless, CGRP1 and NPY Y1 receptors were not found in the OG in one study (121). Unpublished work from Angelov *et al.* has found the OG to have perineuronal synapses positive for choline acetyltransferase (ChaT), glutamate and GABA but not for tyrosine hydroxylase (TH, which is an adrenergic marker) (Figure 6).

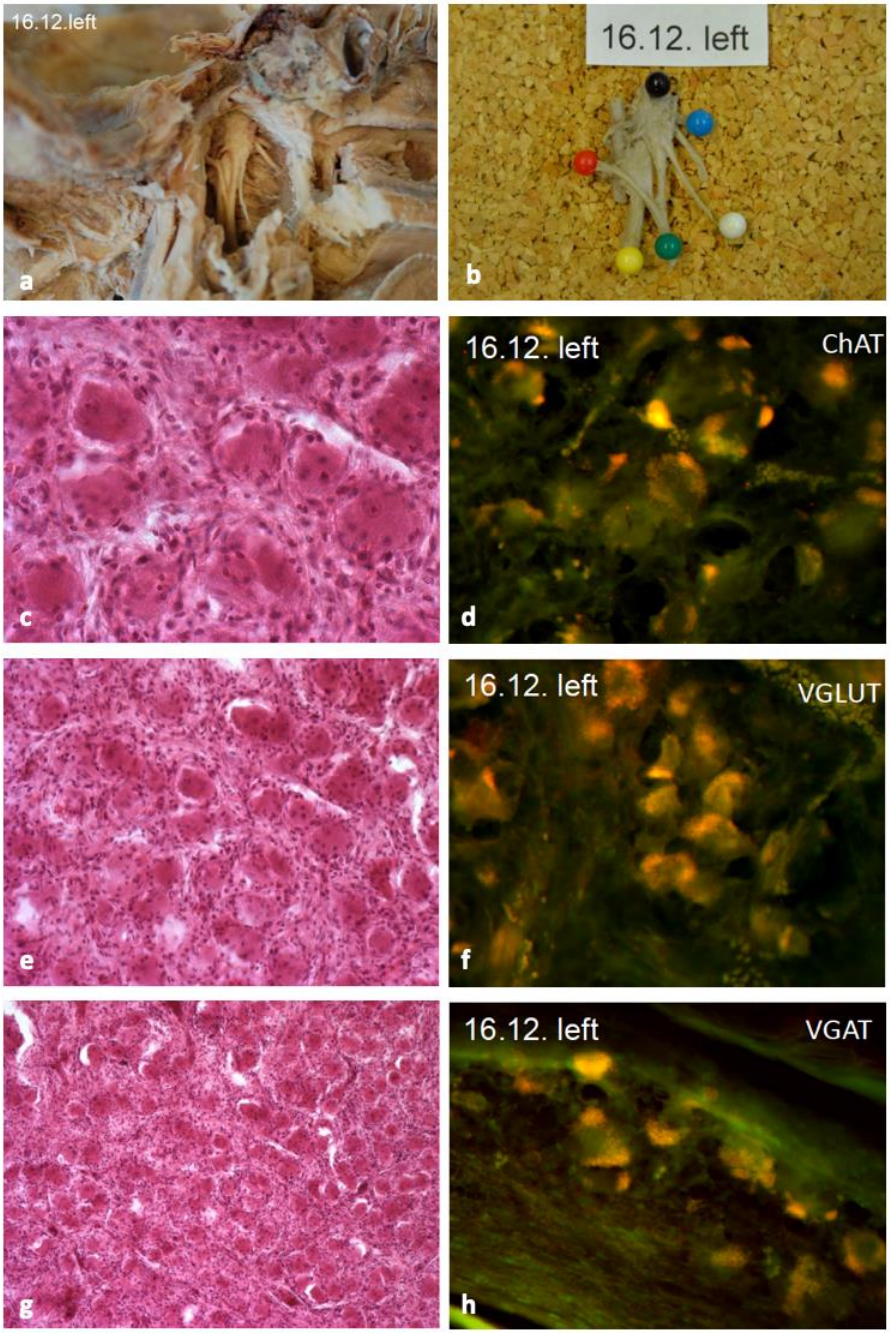


Figure 6: **a.** medial view of one of the cadaveric preparations of the left otic ganglion (OG) presented in paper 3. **b.** dissection of the otic ganglion presented in the previous figure. **c**, **e** and **g**: hematoxylin/eosin staining of the same OG. Immunohistochemical preparations of the same OG for choline acetyltransferase (ChaT, **d**), vesicular glutamate transporter (VGLUT, **f**) and vesicular GABA transporter (VGAT, **h**). With permission of Prof. Angelov D. (unpublished images).

In conclusion, the parasympathetic innervation of intracranial vessels from the OG shown in different animal models (111-113) and in humans (115, 122) and the pathophysiological involvement of the cranial parasympathetic system in primary headache disorders places the OG as an interesting and potentially viable therapeutic target for the treatment of TACs and other headache disorders. The lack of hypersalivation in patients undergoing CH attacks might be related to the complex autonomic dysfunction observed in CH attacks and does not necessarily rule out a possible role of the OG in this condition. Moreover, one should keep in mind that salivation is a complex process where the submandibular and sublingual glands are also involved (innervated via the facial nerve through the submandibular ganglion (123)).

*Botulinum toxin and cranial autonomic ganglia*

Botulinum toxin binds with high selectivity to glycoprotein structures located on the cholinergic nerve terminal (124-126). Botulinum toxin light chain is internalized and cleaves different SNARE proteins (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) (124) which are important for the fusion of the synaptic vesicles with the plasma membrane (126). In the studies presented in papers 2 and 4, botulinum toxin type A was used, which targets SNAP 25 (127).

Since the SPG (128) and the OG contain cholinergic terminals (Figure 6), we expect that BTA can produce a parasympathetic block in these neural structures. Whether BTA might be uptaken by sensory fibers in the SPG or the OG is not known. Retrograde uptake of BTA has been described (129) but its clinical effect is not known. One should keep in mind that much larger doses of botulinum toxin than the ones used in paper 2 and 4 (a maximum of 25 U of BTA) are injected towards different extracranial structures. For instance, in migraine doses of more than 155 U of BTA are injected (130) and CNS toxicity has not been reported.

When BTA is injected intramuscular, the effect starts within 2-3 days and reaches its maximal effect in about 2 weeks (124). The effect starts to decline after 2.5 months (124) and this was originally thought to be due to sprouting (forming of new synapses). Later work has shown that sprouting is a temporary process and that the original synapses are eventually

regenerated (131). The duration of a BTA block in the autonomic system might be longer, up to 3 to 12 months, according to data from studies on hyperhidrosis (132) and injection of BTA towards the SPG (1, 2, 133).

# 7 Aims of study

The aim of this project was to evaluate safety and potential for efficacy of cranial ganglion blocks in two important headache conditions, CH and TN.

Sub aims:

- To develop an algorithm to predict the position of the SPG using bony landmarks depicted in CT-scans (paper 1).
- To evaluate safety and potential for efficacy of blocking the SPG with BTA in patients with classic TN (paper 2).
- To describe the distance between the FO and the OG in order to be able to target this cranial autonomic ganglion (paper 3).
- To evaluate safety and potential for efficacy of blocking the OG with BTA in patients with chronic CH (paper 4).

# 8 Methods

## 8.1 Paper 1

CT-scans and MR-images from twenty-seven patients included in clinical trials targeting the SPG at St Olav's University Hospital from 2013 to 2017 were screened (1, 2, 75). MRI was performed according to our group's protocol for identification of the SPG (4). Only sides where two observers (the author of this Thesis and the second author of paper 1, Daniel Bratbak) were positively certain of the position of the SPG were included.

We first localized the SPG on MRI and the images were then fused with CT-scans (Figure 7).

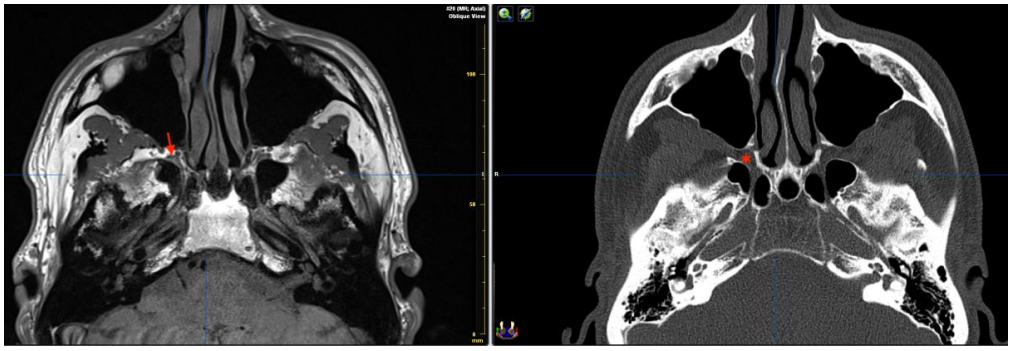

Figure 7: axial MRI (left, T1 sequence) and axial CT-scan at the same plan were fused using Brainlab iPlan 3.0 (Brainlab AG, Feldkirchen, Germany). The red arrow (left image) marks the right SPG. The red star (left image) indicates the position of the SPG on the fused axial CT-scan.

The coordinates of the centre of the SPG and two bony landmarks, the anterior opening of the Vidian canal (VC) and a point on the sphenoidal bone, were calculated. These coordinates were used to measure the distance from the centre of the SPG to these bony landmarks identified on CT-scans. Subsequently, we applied the average distances to predict the position of the SPG for each participant.

The first anatomical landmark (the anterior opening of the Vidian canal) is depicted in Figure 2 in paper 1, and the predicted position of the SPG according to this method was referred to as vcSPG.

The second landmark, a point on the sphenoidal bone, was referred to as S-point (Figure 3 in paper 1).

Figures 15 and 16 under section 10.1 of this Thesis ("Prediction of the localization of the SPG") thoroughly clarify how the position of vcSPG and the S-point were calculated.

## 8.2 Paper 2

In paper 2, a total of 10 patients between 18 and 80 years old with classical TN (according to ICDH-3 Beta criteria) were recruited and treated between September 2015 and October 2018 at St Olav's University Hospital, Trondheim, Norway. Patients had had unsatisfactory effect, intolerable side effects or contraindications to carbamazepine or oxcarbazepine and they had tried at least one of the following drugs: gabapentin, baclofen, pregabalin**,** lamotrigine or phenytoin. Different authors have used different definitions to consider TN refractory to medical treatment. The European Academy of Neurology guideline on TN describes that there is very low quality of evidence to define how many drugs a patient should have tried before being referred to surgery (14). This guideline describes that patients should be offered surgery if "their pain is not sufficiently controlled medically or if medical treatment is poorly tolerated". Other authors have pointed out that the evidence regarding efficacy is limited and that "there is no single answer as to how many medications should be tried out before a TN patient is deemed medically refractory and surgery should be considered" (134). Previous international guidelines described that in case of failure to one of the following drugs: carbamazepine or oxcarbazepine, referral to surgery should be considered (135). Some have considered that failure to only one drug might be "too hasty" and have suggested that one should try out a combination treatment before referring to surgery (134). The evidence for other drugs than carbamazepine or oxcarbazepine (such as pregabalin, gabapentin, lamotrigine or baclofen) or for combination therapy is limited (14, 134).

Inclusion criteria used in paper 2 did not include any lower limit of number of pain attacks for participants. The main reason is that this was a pilot trial were the primary outcome was safety. In a trial were the primary outcome was efficacy it would have been sensitive to include such a lower limit. Even one single attack per day (as patient 8 in paper 2 experienced on average) can be extremely invalidating. A discussion on whether pain intensity might be a more useful efficacy outcome in TN trials can be found in section 10.2 of this Thesis ("Role of the SPG in TN"). The lack of a lower limit of number of paroxysms for inclusion in paper 2 is also discussed in section 10.4 ("Limitation of the studies"). The primary outcome in paper 2

was occurrence of AEs. In this pilot study, our main goal was to establish the feasibility of such a treatment in a group of patients with classical TN (ICHD-3 beta criteria) and gather safety data. The main secondary outcome was the number of TN attacks at weeks 5-8 after injection versus baseline.

A treatment responder in this study was predefined as ≥ 50% reduction in the median number of attacks per day between baseline and weeks 5-8. In such an exploratory pilot trial, where a novel experimental surgical invasive technique was used, we were interested in capturing signals of a strong and clear clinical effect in order to evaluate whether further RCTs were warranted, and this is why a 50% reduction was chosen instead of a 30% reduction rate. As stated under "Limitations of the studies" and under "General Discussion, Role of the SPG in TN", there are no international guidelines for conducting trials in TN and this constitutes a major challenge for clinicians and researchers.

Neurologists visiting headache patients at St Olav's University hospital (Trondheim, Norway) received thorough information about the inclusion and exclusion criteria of the study presented in paper 2 and thus only 22 patients were pre-screened. Twelve patients were screened and two patients were considered screening failures during baseline (one patient had a lesion seen on MRI which was thought to be related to his symptoms and the other patient felt that he had a "good period" so he was not interested in receiving the experimental treatment).

The flowchart used in paper 2 can be seen in Figure 8. There was a baseline of 4 weeks prior to injections. In that period of time, patients had to fill a paper-pencil diary and collect information regarding the number of attacks, intensity, functional level, drugs used and dose, and whether they were away from work because of TN.

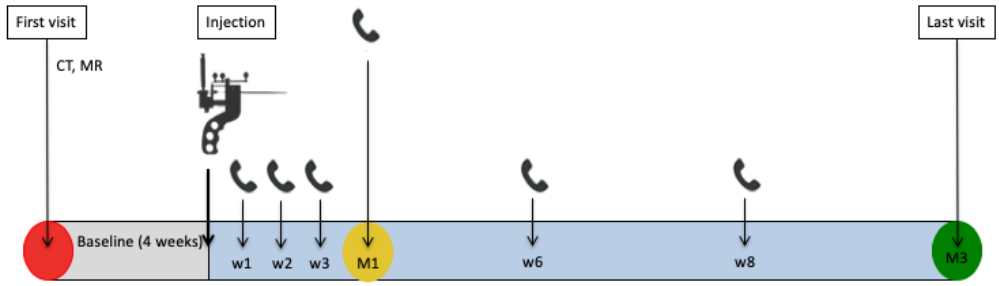


Figure 8: Flowchart of the study presented in paper 2 in which 25 U BTA were injected towards the SPG in patients with classic TN (ICHD-3 beta criteria). Patients were seen by a neurologist at baseline and at month 3 (last visit). Follow up was done by phone consultation at weeks 1, 2, 3, 4, 6 and 8. w: week, M: month.

All phone calls were placed by the author of this Thesis. Whether the patient was recording properly the headache diary was controlled. Patients were asked if they had experienced any side effects after injection (this information was also recorded in the patient's diary). Patients could report freely any new symptom and they were specifically asked whether they had experienced dysphagia or diplopia. The number of days with TN since the last consultation was documented. Patients were allowed to ask any questions during phone calls.

In paper 2, patients were treated using a similar approach as 2 prior pilot studies in other conditions (1, 2). In the first pilot trial (BTA injection towards the SPG in patients with chronic cluster headache), the follow up was 6 months after injection (1). No new AEs were seen 4 weeks after injection and all AEs had remitted at that point. In the second pilot study, where BTA was injected towards the SPG in patients with chronic migraine (2), the follow up was 3 months after injection. Likewise, no new AEs were seen one month after injection and only one patient had an ongoing AE at the end of the study period (temporomandibular joint dysfunction). Thus, we and the local ethical committee that evaluated the protocol, deemed reasonable to have a follow up of 3 months for paper 2.

It is interesting to notice that 2 of the patients had allodynia prior to treatment (Table 2 in paper 2). We did not measure allodynia electrophysiologically but anamnestically (by asking whether non-painful stimuli such as light touch might be experienced as painful) and clinically

(standard neurological examination performed at visit 1). One of the patients (patient 4) had previously been treated with microvascular decompression and glycerol rhizolysis (unfortunately, it was not documented after which one of these treatments allodynia appeared). The other patient (patient 8) had not undergone any surgical treatment. In a prospective systematic study of 158 patients with classical trigeminal neuralgia published in 2014, only 4 patients (3%) had allodynia.

*Classic TN in ICHD-3 beta vs ICHD-3*

ICHD-3 beta was published in July 2013 (136) and ICHD-3 was published in January 2018 (68). The first patient in paper 2 was included in August 2016 and the last patient completed the study in October 2018. Thus ICHD-3 beta diagnostic criteria for classic TN were used in paper 2. There are important differences regarding diagnostic criteria for TN between ICHD-3 beta and ICHD-3. Both editions of the International Classification of Headache Disorders describe TN as "*a disorder characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli*". The definitive 3rd edition adds one diagnostic criterium for classic TN, not specified in the beta version: "*Demonstration on MRI or during surgery of neurovascular compression (not simply contact), with morphological changes[1] in the trigeminal nerve root*" (criterion B for classic TN; "*1: Typically atrophy or displacement*"). The beta version states under "*Comments"*: "*The term* classical *(rather than* primary*) neuralgia is used because, according to current evidence, Classical trigeminal neuralgia is caused by neurovascular compression, most frequently by the superior cerebellar artery. Imaging (preferably MRI) should be done to exclude secondary cause and, in the majority of patients, to demonstrate neurovascular compression of the trigeminal nerve*". Consequently, the beta version of the 3rd edition did not require patients to present atrophy or displacement of the trigeminal nerve in MRI. The definitive 3rd edition includes the nosologic classification of *Idiopathic* TN, not included in the beta version. *Idiopathic* TN is defined as "TN with neither electrophysiological tests nor MRI showing significant abnormalities". A patient with a simple contact between an artery and the trigeminal nerve (i.e. no atrophy or dislocation of the TN) would have been classified as *classical TN* according to the 3rd beta classification but the same

patient would be classified as *idiopathic TN* according to the definitive 3rd edition of the International Classification. The reason for this change in the ICHD 3rd edition was that simple vascular contacts can be often observed in healthy subjects (68). All patients but 1 (patient number 2 in paper 2) had simple vascular contacts with the trigeminal nerve and thus would have been diagnosed as idiopathic TN according to the last and current classification.

All 10 patients included in paper 2 had been examined with MRI and thus it was not necessary to implement the algorithm described in paper 1 in order to predict the position of the SPG in CT-images. When applying this algorithm in these 10 patients with TN, we managed to predict the position of the SPG with high accuracy as compared to the MRI localization of the SPG (unpublished data).

## 8.3 Paper 3

Since the OG cannot be seen in CT-scans or in conventional MR imaging, in order to target this structure in paper 4, we needed to describe its distance to a reliable anatomical landmark: the FO, which can be easily seen in CT-scans.

Twenty-one high definition photographs of 21 infratemporal fossae from 18 cadavers were analysed. Unfortunately, the cadaveric preparations were no longer available for direct analyses since they had been inhumed. For this reason, high resolution photographs were used instead. Spatial resolution of the images (number of pixels utilized in the construction of the image) was 3008 × 2000. This resolution allowed us to measure 0.1 mm differences.

An anatomical study using the same cadaveric preparations was published by Senger *et al* (5). In this study, the topography, syntopy and morphology of the OG were described. However, the distance from the OG to the FO was not reported. The distance between the inferior edge of the medial part of the FO to the center of the OG (Figure 9) was measured using free available software (137).

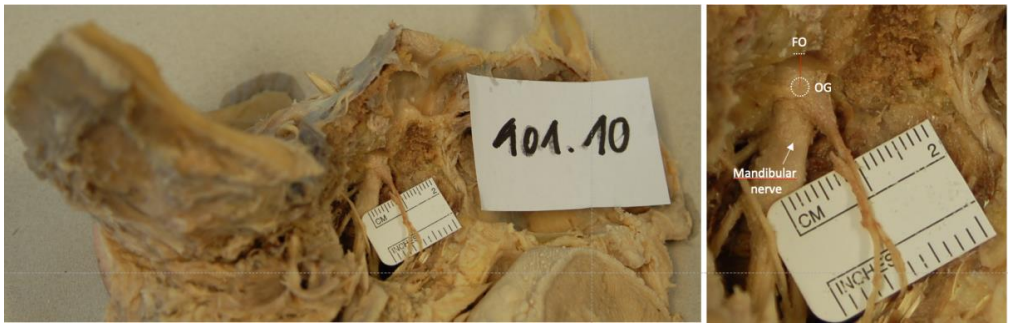


Figure 9: example of one of the 21 anatomical preparations. The left photography shows a medial dissection of the left infratemporal fossa. The right photography shows a magnified detail of the left image. The distance between the inferior edge of the medial part of the foramen ovale (FO) and the otic ganglion (OG) is shown with a red line.

Mean results of the measurements performed by the author of this Thesis and the second author of paper 3 (Daniel Bratbak), SD and range are reported.

## 8.4 Paper 4

In paper 4, a total of 10 patients between 18 and 70 years old with intractable chronic CH (ICDH-3 beta criteria) were recruited and treated between June 2017 and May 2019 at St Olav's University Hospital, Trondheim, Norway. Five patients were injected with 12.5 U of BTA and 5 patients were injected with 25 U BTA towards the ipsilateral OG. The primary outcome in paper 4 was AEs. The main secondary outcome was the number of attacks per week measured at baseline and in month 2 after injection.

As in paper 2, treatment responder in paper 4 was predefined as ≥50% reduction in the mean number of CH attacks per week between baseline and month 2 after injection. In this study, a responder rate of 50% was preferred over 30% due to the same reason as in paper 2: in this exploratory pilot trial, where the OG was blocked for the first time using an invasive surgical experimental technique, we were interested in capturing signals of a strong and clear clinical effect in order to evaluate whether further RCTs were warranted.

Silbertstein *et al.* defined "moderate intractability" in CH as failing at least two drugs (138). In paper 4, we defined intractability as having had insufficient effect, unacceptable side effects or contraindication to at least two of the following drugs: verapamil, lithium or suboccipital steroid injection. The flowchart used in paper 4 is displayed in Figure 10.

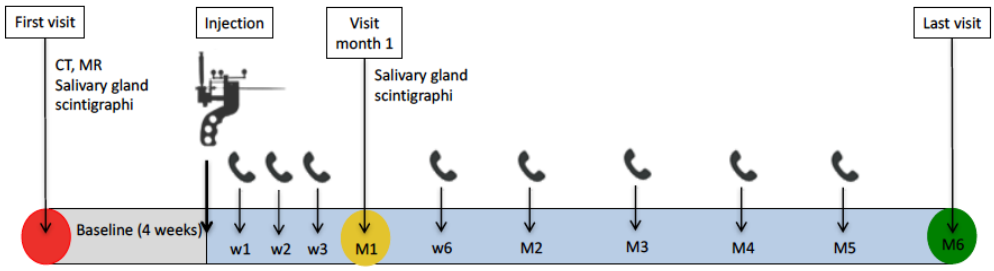


Figure 10: Flowchart used in paper 4, where 10 patients with intractable chronic CH were injected with 12.5 U (5 patients) or 25 U (5 patients) BTA towards the OG. Patients were seen by a neurologist at baseline, month 1 and month 6 (last visit). Follow up was done by phone consultation at weeks 1, 2, 3, 6 and monthly thereafter. w: week, M: month.

Phone calls were placed by the last author of paper 4 (Erling Tronvik), the study nurse or the author of this Thesis. These consultations obtained detailed information on whether the patient was compliant with the headache diary. Side effects after injection and any health problems that should be evaluated were recorded. Patients were asked whether their headache had improved, worsened or remained unchanged after treatment. Patients could report freely any complaint and ask questions to the main researchers throughout the follow-up. Patients could also register side effects in their headache diaries.

Our group evaluated the possibility of performing a salivary scintigraphy prior and after a block towards the OG (as stated in Figure 10) but this could not be included in the study due to logistical problems (see Future perspectives).

Given that the OG had never been blocked before, we decided to follow patients for a longer period of time (6 months after injection) than in paper 2 (3 months after injection).

*Chronic CH in ICHD-3 beta vs ICHD-3*

The first patient included in paper 4 was recruited the 12$^{th}$ of September of 2017. Thus ICHD-3 beta criteria were used throughout the study. The most important difference for chronic CH between ICHD-3 beta and ICHD-3 is the maximum length of time that patients are allowed to have a remission. ICHD-3 beta defines chronic CH as "occurring without a remission period, or with remissions lasting <1 month, for at least 1 year". ICHD-3 defines chronic CH as "occurring without a remission period, or with remissions lasting <3 months, for at least one year". All 10 patients recruited in paper 4 would have also fulfilled ICHD-3 criteria for chronic CH.

Given that the OG cannot be directly identified in CT-scans or in conventional MRI, the methodology described in paper 3 was used in order to plan the treatment. The mandibular nerve was localized on a sagital plane in MRI (Figure 11).

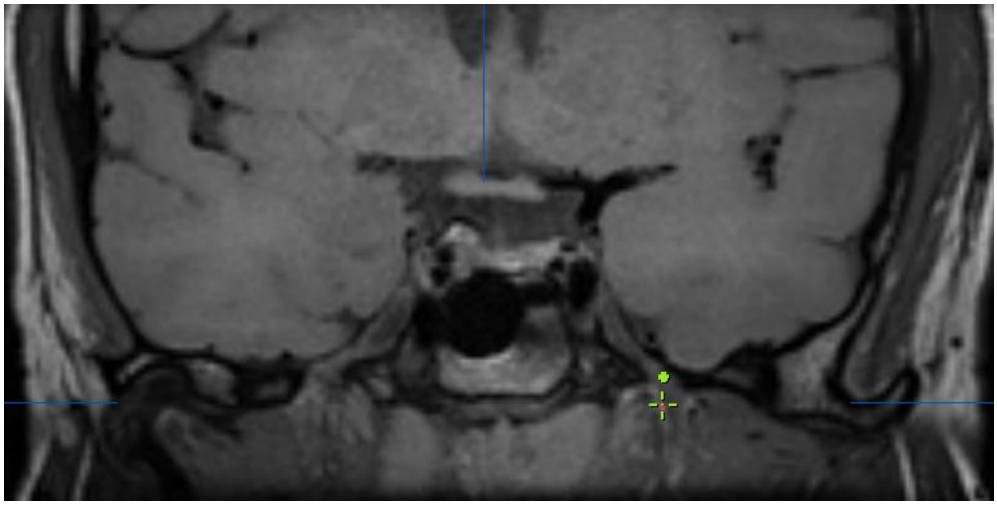

Figure 11: T1 image obtained with a 3-Tesla MRI machine in one of the patients in paper 4. The green dot is situated over the mandibular nerve. The green cross with a red dot in the center is situated over the expected location of the otic ganglion, directly medial of the mandibular nerve. A modified version of this imaged has been published by the author of this Thesis (139).

In paper 3, the mean distance between the inferior aspect of the FO and the otic ganglion was calculated. A sagital CT image through the FO (Figure 12) was fused with the corresponded image to the one displayed in Figure 11, using Brainlab iPlan.

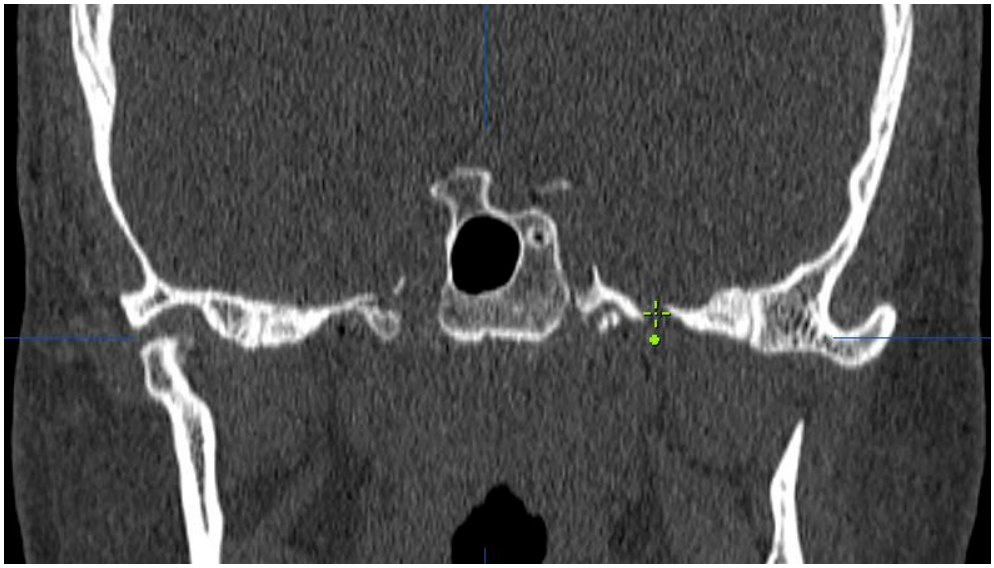

Figure 12: sagital CT-scan through the foramen ovale (FO, green cross) in one of the patients of paper 4. The green dot is situated 4.5mm inferior to the FO, where the OG is expected to be. A modified version of this imaged has been published by the author of this Thesis (139).

Once the OG was localized after fusing the images presented in Figure 11 and 12, a trajectory could be planed. In order to avoid piercing the mandibular nerve, an anterior infrazygomatic trajectory towards the infratemporal fossa, which advances medial to the mandibular nerve was chosen (Figure 13 and 14).

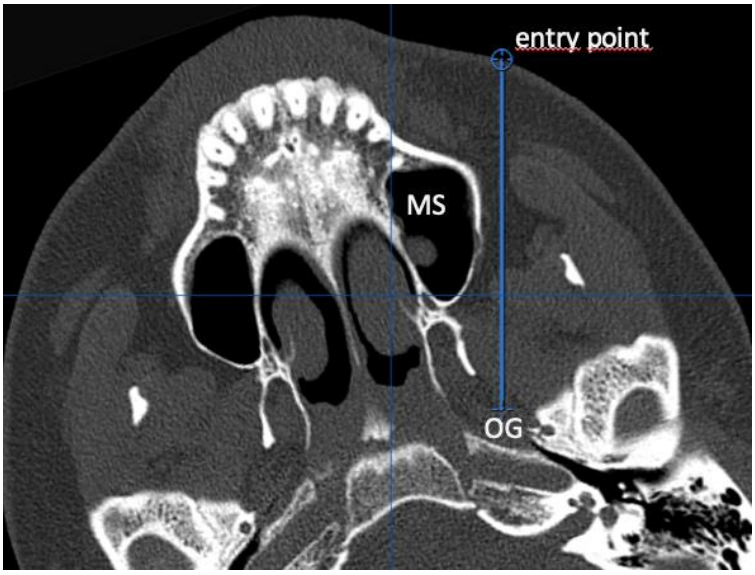


Figure 13: CT reconstruction of the trajectory used to target the otic ganglion (OG) in one of the patients treated in paper 4. MS: maxillary sinus. A modified version of this imaged has been published by the author of this Thesis (139).

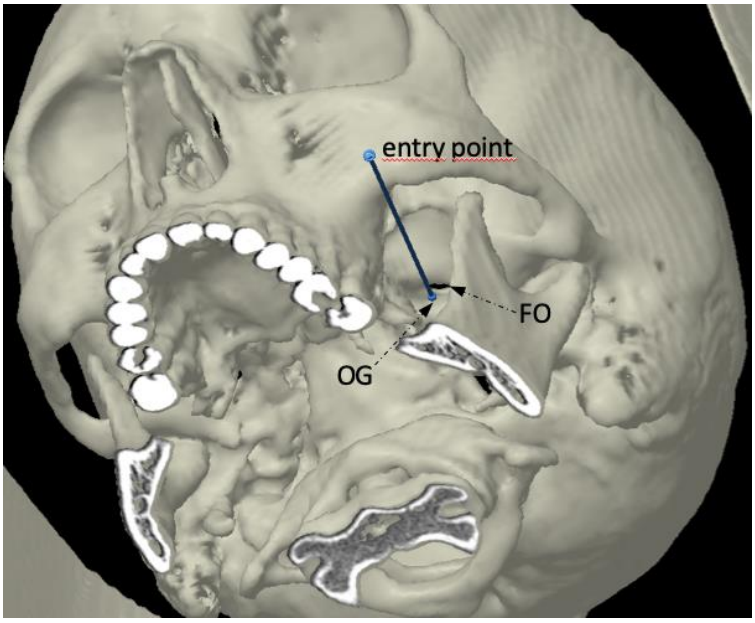


Figure 14: 3D reconstruction of the trajectory used to target the OG in one of the patients in paper 4. FO: foramen ovale, OG: otic ganglion. A modified version of this imaged has been published by the author of this Thesis (139).

# 9 Results – overview of papers

## 9.1 Paper 1

**Prediction of the sphenopalatine ganglion localization in CT images**

The SPG cannot be seen in CT-scans and its localization in MRI is not standard in clinical practice. Being able to predict the localization of the SPG in CT-scans would be advantageous for those interested in targeting this neural structure in several conditions. For this reason, we measured the distance between to bony structures that are easy to localize in CT scans and the SPG (localized in MRI). Then we developed an algorithm in order to predict the SPG's localization. These two bony landmarks were the anterior opening of the Vidian canal and a point on the sphenoidal bone. The SPG's predicted position as measured from the anterior opening of the Vidian canal was referred as vcSPG. The SPG's predicted position as measured from a point on the sphenoidal bone was referred as sSPG. Finally, we measured the distance between our predicted position of the SPG to the position of the SPG as seen in MRI.

The average distance between SPG as seen on the MRI images and the estimated position based on CT images were 1.82 mm (SD: 0.83, range 0.22-3.57mm) for vcSPG and 2.09 mm (SD: 0.99, range 0.71-4.79mm) for sSPG.

**Conclusions of paper 1**

The SPG's localization can be predicted on CT-scans using bony landmarks. The bony landmarks used in this study were the anterior opening of the Vidian canal and a point on the sphenoidal bone. The anterior opening of the Vidian canal appears to be more useful and easier to implement than the point on the sphenoidal bone. The prediction of the SPG's topography can be helpful in those clinical and research settings when one attempts to target this cranial autonomic structure.

## 9.2 Paper 2

**Pilot Study of Injection of OnabotulinumtoxinA Toward the Sphenopalatine Ganglion for the Treatment of Classical Trigeminal Neuralgia**

Ten patients with classical TN (according to ICHD-3 beta criteria) were injected with 25 U of BTA towards the ipsilateral SPG. These patients had tried carbamazepine or oxcarbazepine and at least one of the following: gabapentin, baclofen, pregabalin, lamotrigine, and phenytoin.

Data for all 10 patients was obtained and analysed for the primary endpoint (AEs). There were a total of 13 AEs in 6 of the 10 patients. None of the AEs were severe. The following AEs were observed: pain or swelling at the injection side (3 patients; all resolved within 4 weeks after treatment), jaw problems (4 patients; last patient became symptom free 4 months after injection), nasolabial fold asymmetry (2 patients; both resolved 4 months after injection), diplopia (1 patient; resolved 4 months after injection), dry eye (1 patient; resolved 4-12 weeks after injection), discomfort swallowing (1 patient; resolved <4 weeks after injection) and rash (1 patient; resolved a few days after injection). Among the 3 patients who had pain, only one needed extra analgesics (paracetamol) on the same day of the injection. All other AEs did not require any specific treatment. All reported AEs were considered mild with the exception of diplopia, which affected moderately the patient's daily activities. Diplopia appeared in a patient with a considerably thin sphenopalatine fossa and we believe that BTA reached the inferior rectus muscle through diffusion along the inferior orbital fissure.

In paper 2, the median number of TN attacks during the 4-week baseline and weeks 5-8 after injection (main secondary outcome) was 5.5 (range: 1.0 – 51.5) and 5.0 (range: 0 – 225.0) respectively ($p = 0.401$).

The PGIC (Patient Global impression of Change) was: “very much improved” in 1 patient, “much improved” in 2 patients, “minimally improved” in 2 patients, “no change” in 2 patients and “minimally worse” in 3 patients. None of the patients had a PGIC “much worse” or “very much worse”.

Four patients were treatment responders (≥50% reduction in the median number of attacks per day between baseline and weeks 5-8). The median intensity of attacks at baseline and weeks 5-8 after injection was 6.0 (range: 3.0 – 8.5) and 3.0 (range: 0.0 – 9.0) respectively (p=0.024). The median functional level at baseline was 2.0 (range: 1.0 – 3.3) and at month two, 1.0 (range 1.0 – 4.0; p= 0.750). Median percentage of the day with concomitant persistent pain was 75% (minimum 37.5%, maximum 100%) at baseline and 18.8% (minimum 0%, maximum 100%) at week 8 (p=0.023).

**Conclusions of paper 2**

In the 10 patients with classical TN (ICHD-3 beta criteria) included in paper 2, injection of 25 U BTA towards the SPG using a new image guided technique (the MultiGuide®) was considered to be safe and well tolerated. The main secondary endpoint of the study (reduction in the number of attacks from baseline to weeks 5-8) was negative. The role of the SPG in TN needs to be better established.

## 9.3 Paper 3

**Anatomical landmarks for localizing the otic ganglion, a possible new treatment target for headache disorders**

The OG might become a target in headache disorders. This small cranial autonomic ganglion cannot be seen in CT-scans or in conventional MRI. In order to aid navigation-based strategies that aim to target the OG, we described its distance to the foramen ovale.

Measurements were performed on photographs of 18 cadavers. Twenty-one infratemporal fossae were available for analysis. Unfortunately, we were unable to localize the inferior edge of the foramen ovale precisely in 4 photographs and thus these photographs were excluded. A total of 15 infratemporal fossae were measured.

The mean distance from the foramen ovale to the OG was 4.5 mm (SD 1.7), range 2.1 – 7.7 mm.

**Conclusions**

In paper 3, we have measured the average distance from the foramen ovale, which is an easily identifiable anatomical landmark that is visible in CT-scans, to the centre of the OG. Future studies trying to target the OG might benefit from the topographical description presented in this study.

### 9.4 Paper 4

**Open-label, multi-dose, pilot safety study of injection of onabotulinumtoxinA towards the otic ganglion for the treatment of intractable chronic cluster headache**

Ten patients with intractable chronic CH (ICHD-3 beta criteria) were injected with 12.5 U (5 patients) or 25 U BTA (5 patients) towards the ipsilateral OG. Patients had had unsatisfactory effect, intolerable side effects or contraindication of at least two of the subsequent medications: verapamil, lithium or suboccipital steroid injection.

The primary endpoint in paper 4 was the occurrence of AEs. 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. Pain or swelling at injection side (3 patients), jaw problems (1 patient), chin numbness (2 patients), and subjective articulation difficulties (1 patient) disappeared within the first 4 weeks after injection. Discomfort swallowing in one patient (without dysphagia) disappeared at month 2 after injection. Tinitus was referred by one patient and disappeared at month 3. Ear fullness was present in two patients (it disappeared at month 1 and month 3 respectively). None of the 2 patients who referred nasal voice had an abnormal neurological examination (specifically no dysarthria or deficits in palatal elevation). None of these 2 patients had dysphagia. Nasal voice was considered both by patients and by researchers to be mild and did not interfere in daily activities. This symptom disappeared at month 3 after injection in one patient and at month 5 in the other. One patient reported hyperacusis, which ceased at month 6. Dry mouth was reported by 3 patients and it resolved at months 1, 4, and 6 respectively.

Only 3 patients had to use analgesics due to pain at the injection site, which disappeared 1 week after injection. Two patients used recommended doses of paracetamol and 1 patient preferred diclofenac. Analgesics in these 3 patients were used for a maximum period of time of two days after treatment. None of the other AEs required specific treatment.

The main secondary outcome was the number of CH-attacks per week. The median number of attacks per week at baseline was 17.0 (7.8 to 25.8) versus 14.0 (7.3 to 20.0) in the second month following injection; difference: 3 (95% CI: -0.3 to 7.9), p = 0.063.

Only one patient in this study had ≥50% reduction of the number of attacks at month 2 versus baseline (patient 4) and was thus considered a treatment responder.

**Conclusions**

In this cohort of 10 patients with intractable CH, injection with 12.5 U or 25 U BTA towards the ipsilateral OG appears to be safe. The reduction of the number of attacks per week at month 2 after injection compared to baseline (main secondary outcome) was not statistically significant.

In this study we did not find a clear indication that the OG might be a significant target for the treatment of chronic CH. We cannot be certain that BTA reached the OG since this structure was not localized directly. Further work should assess the possible role of the OG in CH. The development of better radiological techniques able to depict the OG should precede further studies targeting this ganglion.

# 10 General discussion

## 10.1 Prediction of the localization of the SPG

We have predicted the position of the SPG using CT images (paper 1). For this purpose, two bony landmarks were used: the anterior opening of the Vidian canal (Figure 15) and a point in the sphenoidal bone (Figure 16). The distance between these two landmarks and the SPG was measured in a total of 38 sides in 21 patients. These distances were used to produce an algorithm to predict the SPG without the need of MRI.

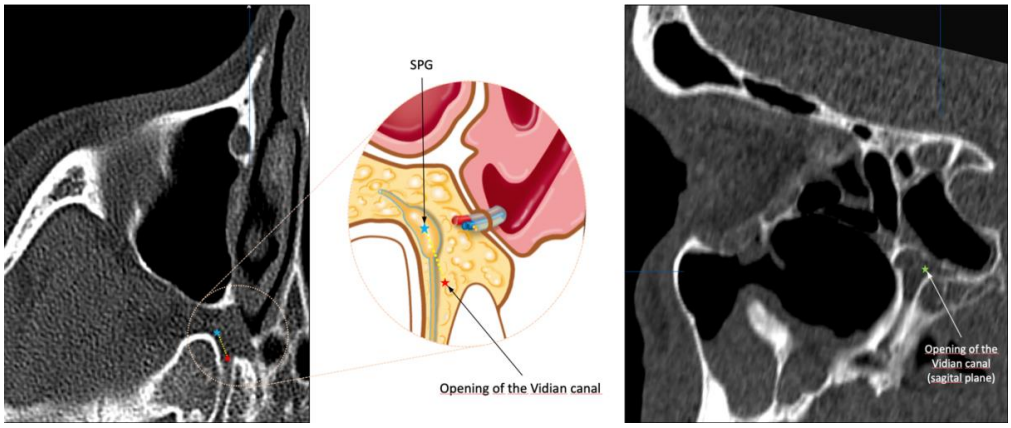


Figure 15: Left image: Axial CT-scan at the level of the anterior opening of the Vidian canal (VC, red star); the blue star shows the localization of the SPG previously localized in fused MRIs. The distance between the opening of the VC and the SPG was measured using Brainlab iPlan 3.0. (here represented with a yellow discontinued line). Middle: this image displays a magnified representation of the left image. Right image: Parasagittal CT-scan at the level of the opening of the Vidian canal (green star). This illustration appears as Figure 2 in paper 1 (39); permission has been obtained from the publisher.

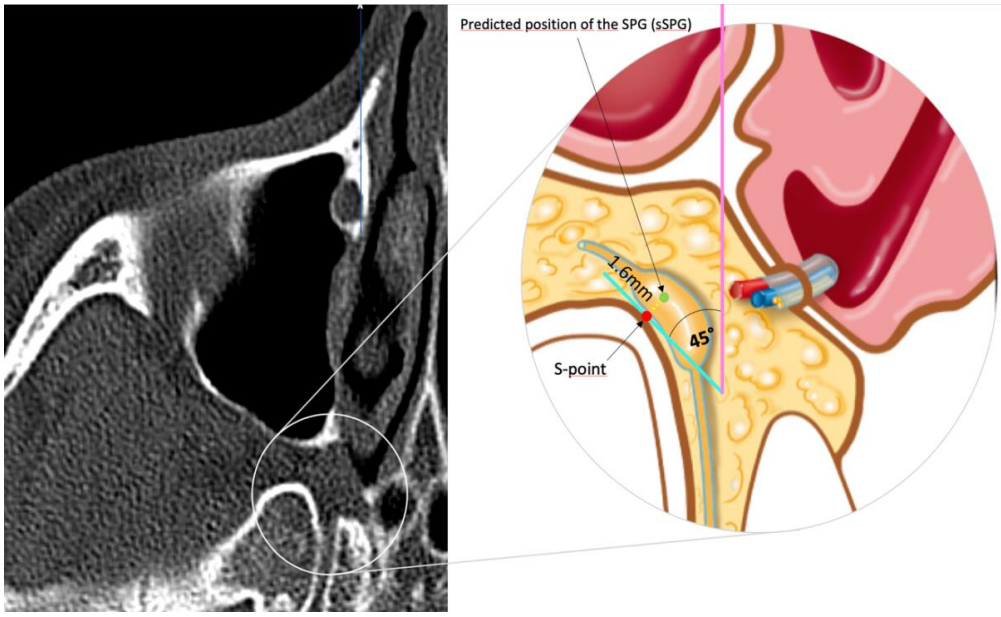


Figure 16: the image on the left shows an axial CT-scan at the level of the opening of the Vidian canal (augmented representation on the right). A parasagittal line is drawn (pink line). Then a line at 45° to this pink line is positioned as a tangent on the curvature of the sphenoidal bone laterally to the VC (cyan line), and the point of contact with the cortex of the sphenoidal bone is registered as the S-point (red point). The predicted position of the SPG (green point, referred as sSPG) was 1.6 mm from the S-point on the discontinuous yellow line (perpendicular to the cyan line) and 1.0mm inferior to the S-point. SPG: sphenopalatine ganglion. This illustration appears as Figure 3 in paper 1 (39); permission has been obtained from the publisher.

As shown under results, the distance between the true MRI-verified position of the SPG and the estimated position of the SPG based was 1.82 mm (range 0.22 – 3.57 mm) based on the anterior opening of the Vidian canal, and 2.09 mm (range 0.71 – 4.79). The mean difference in the distances between the estimated position and the true position of the SPG obtained from the two methodologies was small (2.09 – 1.82 = 0.27 mm). The range difference between the two methodologies was also little ((4.79 – 0.71) – (3.57 – 0.22) = 0.73 mm broader for the measurement based on the sphenopalatine bone). Despite these small differences, we found that the methodology used to predict the position of the SPG based on the anterior opening of the Vidian canal was more straight forward and easier to use in clinical practice. Whether this degree of accuracy is enough might depend on the technique used to target the SPG. For instance, if one is to inject a drug towards the SPG, 4-5mm will be overcome by diffusion of most drugs. Nonetheless, even with the possible error using the methodology described in

paper 1, one will most likely be closer to the real position of the SPG than targeting this structure blindly or based on old unvalidated anatomical landmarks as many groups do (3).

The technique to localize the position of the SPG presented in paper 1 is being used in a multicentre international placebo-controlled trial injecting 25 U BTA or placebo towards the SPG in patients with intractable chronic CH (ClinicalTrials.gov Identifier: NCT03944876) and in a randomized, double-blind, cross- over, placebo-controlled pilot study injecting BTA towards the SPG in patients with Persistent Idiopathic Facial Pain (PIFP, ClinicalTrials.gov Identifier: NCT03462290). Localizing the SPG on CT-images will be valuable when access to MRI is limited, for those patients with contraindications for an MRI and in those where repeated injections are needed (39). When possible, localizing the SPG directly with MRI might be a better option. In addition to the possible error that one would face when using the methodology described in paper 1, one should add the error inherent to navigation-based techniques if those are used.

### 10.2 Role of the SPG in TN

The study presented in paper 2, where we injected 10 patients with classical TN (ICHD-3 beta criteria) with 25 U BTA towards the ipsilateral SPG, was negative for its main secondary endpoint (reduction of number of attacks at weeks 5-8 after injection versus baseline). There are no properly validated SPG-block biomarkers, so the degree of SPG block could not be assessed. None of the previous studies that have tried to block the SPG in TN have documented target engagement (Table 3). The validation of one or several biomarkers of target engagement of the SPG in TN would be extremely valuable for the development of further studies examining the role of this ganglion in this pain condition. We believe that such a validation of biomarker/s should precede further studies targeting the SPG in TN.

The SPG innervates parasympathetically the lacrimal gland and controls lacrimation (140). Lacrimation can be examined using the Schirmer's test (140). This ophthalmological test uses blotting paper to collect tears in a non-invasive manner. We have tried to use this technique

as a biomarker for an SPG-block but we have faced several methodological challenges with this test which is rather rudimentary (unpublished data).

Changes in heart rate variability have been shown in patients with CH who received either low-frequency or sham SPG-stimulation (141). The differences found in this article in heart rate variability might be difficult to implement in clinical practice since differences reported were minimal. Moreover, it is not clear that SPG-stimulators produce a block of the SPG (39).

The parasympathetic system is involved in the trigeminal vascular response (119). The SPG has been involved in intracerebral blood hemodynamics both in animal models and in humans (142-144). Parasympathetic post-ganglionic fibres from the SPG innervate cranial vasculature ipsilaterally (113), causing dilatation when activated (145, 146). We have tried to use Doppler/ultrasound of the supraaortic arteries and transcranial Doppler/ultrasound of the intracranial arteries in a group of patients undergoing a block of the SPG with BTA. We did not manage to find any hemodynamic differences pre- and post-treatment in 10 patients (preliminary data, unpublished). The trigeminal vascular response appears to be important under certain conditions, but not under a basal status (120) and this might be the reason why we have not found any differences in our unpublished preliminary data.

In paper 2, a reduction in concomitant persistent pain in patients with classical TN (ICHD-3 beta criteria) was observed. The underlying pathophysiological mechanism responsible for the reduction in concomitant persistent pain observed in paper 2 could either be related to a role of the SPG in pain sensitization (76), regression to the mean or placebo effect (see section 10.4, Limitation of the studies). An SPG block could reduce the parasympathetic output from the ganglion. This could consequently reduce sensitization and activation of central nociceptive neurons in the spinal trigeminal nucleus and intracranial nociceptors. If the positive findings observed in paper 2 were truly due to an SPG block, we could hypothesize that it is reasonable to expect a reduction in concomitant persistent pain and intensity of the paroxysms, but not of the total number of attacks, as we did observe in this study.

Concomitant persistent pain is very prevalent in TN (77). In paper 2, all 10 patients had persistent concomitant pain at baseline (median percentage of the day 7%, minimum 37.5%,

maximum 100% of the day). The relationship between concomitant persistent pain and paroxysmal pain in TN is not clear. Our own clinical experience agrees with other studies which have shown that concomitant persistent pain can develop before the onset of paroxysms (77, 147). On the other hand, other authors belief that concomitant persistent pain develops in longstanding cases of TN (136, 148).

Once biomarkers of an SPG block are properly established, given that paper 2 showed a favourable AE profile and some positive signals were observed, we believe that it would be interesting to move forward with an RCT. Unfortunately, there are no international guidelines for conducting controlled trials in TN. Thus, it is not straight forward which would be the most appropriate primary outcome. In one of the first RCTs using carbamazepine in TN, a primary endpoint was not prespecified, but severity of pain (divided in 4 categories) was used in order to assess efficacy (149). This paper reports that it was not possible "to keep to exact numerical answers to questions about the number of paroxysms". For this reason, the number of attacks was categorised from 0 (none) to 3 ("every half hour", "innumerable", "hundreds"). Chuan-Jie Wu *et al.* used pain severity assessed by the visual analogue scale as primary endpoint in a study of BTA for the treatment of TN (9). In another study examining the effect of two doses of BTA for the treatment of TN by Zhang H. *et al.* (12), both pain severity using VAS and pain attack frequency were recorded. In this positive RCT, the proportion of responders was predefined as patients with ≥50% reduction in mean pain score from baseline to endpoint. In the results section, information on pain attack frequency is not provided (12) and conclusions are based on information from changes in VAS before and after treatment. In a recent RCT examining safety and efficacy of a Nav1.7 selective sodium channel blocker in patients with TN published by Zakrzewska *et al.* (13), the primary endpoint was defined as follows: "difference between groups in the number of patients classified as treatment failure during the double-blind phase, assessed centrally (the central committee that adjudicated the primary endpoint in a masked manner [before database unlock and unmasking] comprised members of the study team: from the funder, ST, JP, and KG); from the contract research organization, the statistician, study manager, and medical monitor)". In this study, "treatment failure" was defined by meeting at least one of the following criteria: ">3 paroxysms in 7 days and either a 50% increase or more in the severity of paroxysms, compared with the final 7 days of open-label treatment; PGIC of much worse or very much worse (relative to the end of

the open-label phase); or the patient discontinued because of an absence of efficacy (as defined and reported by the patient or clinician), or because of an AE or poor tolerability considered to be related to the study medication" (13). We believe that primary endpoints in TN studies should be more straightforward. Based on the problems that different authors have reported when counting TN paroxysms, pain intensity might be an easier primary endpoint to implement. In paper 2, all but one patient managed to count and register their paroxysms, but this might be more challenging in trials including a larger number of patients. None the less, some authors have used newer technologies such as smart watches or applications in smart phones that make it easier for patients with TN to register their paroxysm. Patient Global Impression of Change (PGIC) has been used in recent studies and might be a valuable endpoint in TN studies (9, 12, 13, 75). Further RCTs should also clarify whether there might be differences between idiopathic and classical TN (ICHD-3 criteria) in response to an SPG block with BTA.

*AE's profile of paper 2 compared to other similar studies*

Bratbak *et al.* injected 10 patients with intractable chronic migraine with BTA towards the SPG (2) using the same technique as in paper 2. In that study, patients were injected bilaterally, while in paper 2 patients were only injected ipsilateral to the pain. Neither Bratbak's study in chronic migraine, nor the study presented in paper 2, recorded any severe AEs. The AE profile in both studies was similar and the most common AE was pain or swelling at injection side, which typically remitted a few weeks after injection.

The same group injected 10 patients with intractable chronic CH with BTA towards the SPG (1). In that study, patients were injected using the same device as in papers 2 and 4 (the MultiGuide®). All patients but one were treated with a transnasal approach (only one patient received a lateral approach). Thus, the AE-profile of this study is not comparable to the study presented in paper 2.

Both pilot trials by Bratbak *et al.* where BTA was injected towards the SPG in chronic CH and in chronic migraine (1, 2) showed positive signals in different secondary efficacy endpoints

and further RCTs were warranted (which are currently ongoing). This was not true for paper 2 presented in this Thesis. Considering the limitation of pilot uncontrolled studies, we could speculate that the SPG appears to be less important in the pathophysiology of TN than in CH and migraine. We consider that more preclinical studies examining the role of the SPG in TN are needed before targeting this structure in further clinical trials.

### 10.3 Role of the OG in CH

We have hypothesized that the loop described previously (between the trigeminocervical complex and dural vessels, Figure 1) is more complicated (37). Besides the projections from the SPG, the output of this loop may also include an additional efferent pathway: fibres from the inferior salivatory nucleus projecting via the glossopharyngeal nerve to the OG (Figure 17)(37).

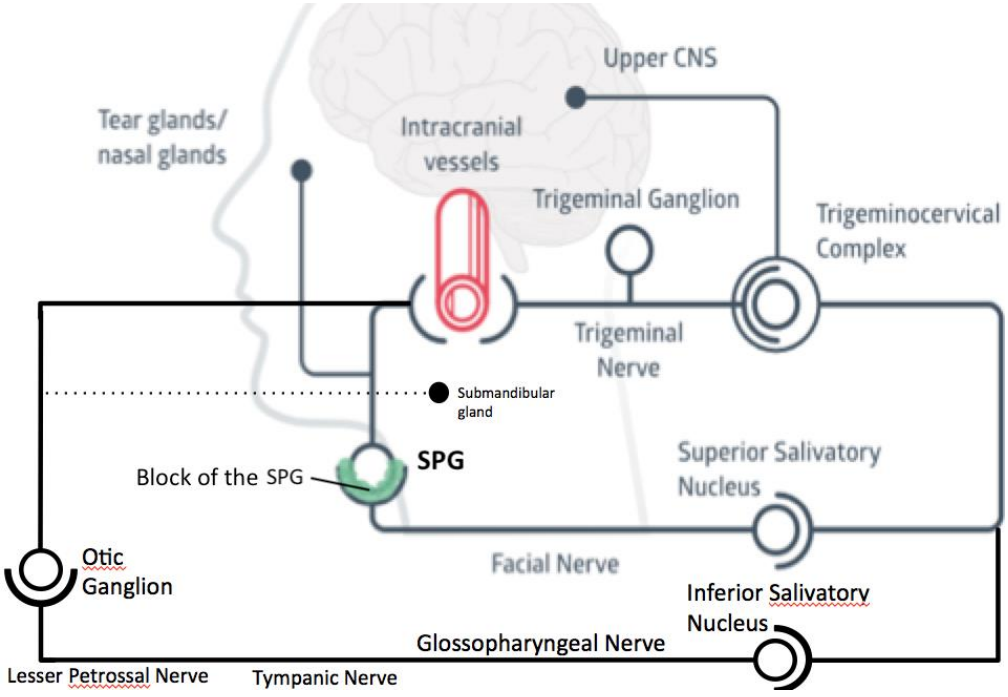


Figure 17: image presenting our hypothesized loop between the trigeminocervical complex and dural vessels, involving the SPG and the otic ganglion. CNS: central nervous system; SPG: sphenopalatine ganglion. Modified illustration with permission of Erling Tronvik. This illustration has been previously used in another publication by the author of this Thesis (37); permission has been obtained from the publisher.

The SPG was removed (histologically confirmed) in 13 CH patients in one study (48). No or only modest clinical effect was observed in that study: 7 patients reported no effect, 4 patients reported incomplete relief and just 2 patients reported relief over the following year. We hypothesize that the parasympathetic output from the OG could be sufficient to maintain the positive feedback system to activate trigeminal nociceptive afferents through the same mechanism as SPG efferents (37). The model presented in Figure 17 could explain the lack or partial response when the SPG is resected, radiated (e.g using gamma knife), or blocked using different drugs (37).

Notwithstanding the studies that have implicated the OG in the pathophysiology of the trigemino-autonomic system, the SPG has remained the only parasympathetic cranial ganglion targeted in headache disorders until our study presented in paper 4. The reason could be that the SPG has a bigger size than the OG, that the SPG's location is better documented or due to a common believe that the SPG is more accessible for interventions (3).

In paper 4, 12.5 or 25 U of BTA were injected towards the OG in 10 patients with intractable chronic CH and the main efficacy outcome (number of attacks per week measured at baseline and in the second month following injection) was negative. Only 1 patient was a responder (≥50% reduction of attack frequency compared to baseline). A pilot trial in 10 patients with intractable chronic CH where 25 or 50 U BTA were injected towards the SPG (1) was positive for the same efficacy outcome and 5 out of 10 patients were responders (≥50% reduction of attack frequency compared to baseline). It is interesting to compare these two trials targeting the same population of patients. The SPG was localized directly in MRI images while we used indirect landmarks to localize the OG. Lower doses of BTA toxin were used towards the OG than towards the SPG due to safety concerns. There is more literature backing the involvement of the SPG in CH pathophysiology than literature backing the involvement of the OG. Nonetheless, these methodological aspects stated above might have had a negative impact on the result of the pilot trial targeting the OG.

The use of biomarkers to confirm target engagement in paper 4 could have improved the results of the study. Parasympathetic fibres exiting the OG innervate the parotid gland and

the smaller buccal glands. Salivary production can be measured using different techniques (117, 150). One could speculate that even if a complete block of the OG is achieved, one could not measure a decrease in the total salivary production since the contralateral parotid gland or the submandibular glands might compensate for the reduced production of saliva. Thus, a direct measurement of the salivary flow from the ipsilateral parotid gland should be planned if one wanted to use salivary flow as a biomarker for target engagement after a block of the OG. This might be technically challenging and one should consider that in single individuals, there may be considerable asymmetry in salivation (117). Three out of 10 patients in paper 4 experienced dry mouth that resolved <4 weeks, by month 4 and by month 6 respectively after injection of BTA towards the OG.

Salivary gland scintigraphy using (99m)Tc-pertechnetate can be used as a semiquantitative analysis of salivary flow (151). This technique could potentially be used as a biomarker for target engagement in future studies targeting the OG.

### 10.4 Limitations of the studies

*Paper 1*

The main limitation of this study is the small number of patients included in order to produce an algorithm to predict the position of the SPG in CT-scans (21 patients). This algorithm will have to be validated in a larger more ethnically varied sample, since all patients were white Caucasians and there was a predominance of females (only 7 males were included in paper 1). Age of the patients was not taken into consideration. It is not known whether normal aging might produce small changes in the topography of the SPG that might be clinically significant.

Our proposed method was dependent on the previous localization of the SPG in MRI and this methodology has not been validated by other groups (4).

The fact that the SPG does not always appear as a single macroscopic structure (152) constitutes a limitation for this study.

*Paper 3*

As in paper 1, the sample included in this paper was small (21 infratemporal fossae from 18 cadavers). The distance between the FO and the OG should be validated in a larger more ethnically varied sample (all cadavers were white Caucasians). Gender and age had not been labelled in the anatomical preparations and this might be important in order to better assess the location of the OG.

Measurements were performed in cadavers and not in vivo. The measured distance between the FO and the OG may have changed due to postmortem desiccation or during the anatomic preparation (e.g. due to mechanical factors related to preparation for photography).

All cadavers had been inhumed and therefore it was not possible for our group to analyse directly the anatomical preparations.

*Pilot studies (Papers 2 and 4)*

In both studies presented in papers 2 and 4 target engagement was not assessed using biomarkers. Currently there are no properly validated biomarkers to confirm that a block of the SPG or the OG has been successful. We have assumed that BTA can be taken up in the parasympathetic synapses in the SPG and the OG but this has not been proven in preclinical studies. The minimal dose of BTA necessary to block the SPG or the OG is not known. All these aspects stated above might have influenced that the primary efficacy endpoint in both studies were negative.

Both studies had a small number of patients (10 patients in each study). A small number of patients appears to be a reasonable approach in pilot safety studies, but it also constitutes an

important limitation. A pilot study is defined as a "small-scale test of the methods and procedures to be used on a larger scale" (153). In pilot studies, one attempts to answer "Can I do this?" rather than "Does this intervention work" (154). One should be careful when one uses pilot trials to assess safety. Because of the small sample sizes typically used in pilot trials, uncommon complications might not be captured. Focusing on feasibility and acceptability rather than attempting to assess safety of a treatment when using pilot trials might be more accurate from a methodological perspective (154).

Both pilot studies were open-label studies, i.e. none of the studies had a placebo group. Some of the positive effects observed in these studies might have been due to placebo effect, due to natural fluctuation of disease activity or regression to the mean. Placebo effect might be of a bigger magnitude in interventional studies as compared to medical drug trials (155, 156).

All 20 patients reported in paper 2 and 4 were all white Caucasians. The SPG lies deep in the sphenopalatine fossa (34) and its localization might vary between individuals (3). The only study that has depicted the SPG in living humans (4) and the only study that has tried to predict the location of the SPG in CT-images (paper 1 of this Thesis) examined white Caucasians only. Future studies targeting the SPG will have to include bigger and more ethnically varied human samples.

In paper 2 and 4, headache-data was collected using a paper-pencil diary. Using an electronic diary would have decreased chances for recall bias and facilitated attack registration. This might be especially important in patients with TN, since patients might suffer from many short-lasting severe attacks per day which might be difficult to register (as patient number 9 in paper 2). This problem has been pointed out in another recent trial in TN (13).

Indirect landmarks for the position of the OG were used, and we cannot be sure that the BTA reached the OG. Even though the OG appears to have a constant relation to its neighbouring structures, some of the anatomical variations described by Senger M. *et al.* (5) might have had a negative impact in this study.

In paper 2, a lower limit of number of pain attacks for patients with classic TN (ICHD-3 beta criteria) undergoing an SPG block was not included. For instance, a recent study in classical TN had as an inclusion criterion that patients should experience ≥3 attacks per day (13). Applying this criterion in our data for a *post hoc* analysis would exclude 3 patients (patient 4, 8 and 10). Analysing data from the 6 remaining patients with ≥3 attacks per day (patient 9 had no available data from the headache diary), the primary efficacy endpoint was also negative ($p = 0.345$).

In paper 2, the neurologist involved in performing the treatment was also involved in collecting data on AEs and efficacy. This might have constituted an important bias in this study. In paper 4 the first author was also involved in the treatment and follow up and thus the same bias might be present.

Another important limitation while conduction trials in TN is the lack of international guidelines on this matter.

# 11 **Future perspectives**

Additional work studying the SPG's role as a target for the treatment TN is needed. Better biomarkers both for CH and TN are needed. In the SPG the parasympathetic signalling uses mostly acetylcholine, vasoactive intestinal peptide (VIP), pituitary adenylate cyclase activating polypeptide (PACAP) and nitric oxide synthase (NOS) (128). Another important substance in the trigemino-vascular system is CGRP. These substances are potential biomarkers and thus it will be interesting to measure its levels before and after performing an SPG-block. The neurokinin peptide family, which includes substance-P, could also be an interesting biomarker in pain transmission. Concerns about the methodology used to measure different peptides have also been raised (157). Moreover, it has been discussed whether it is better to measure peptides such as CGRP in jugular blood rather than in peripheral blood (158). These methodological concerns will have to be considered when developing future protocols to detect biomarkers to prove target engagement of cranial parasympathetic ganglia. This validation of biomarkers would have important implications: it would improve the understanding of the underlying mechanisms of headache disorders such as CH or TN, and it could be important for development of new treatments. Nowadays, some patients with CH are referred to invasive procedures towards the SPG without any biological confirmation of target engagement and without any means to predict patient response. Validated biomarkers for an SPG block could potentially provide a tool to identify predictive factors for response.

*The future of TN*

It is not clear how many pharmacological agents a patient with TN should have tried before being referred to surgery (14). There is a lack of studies comparing head to head surgical options for patients with TN who do not respond to pharmacological treatment or for those who have unacceptable side effects. There is a clinical need of better guidelines for evidence-based treatment in TN and more user-friendly standardized tools to register attacks in TN trials. International guidelines for the conduction of trials in TN should be developed.

*The future of the OG in headache disorders*

To enable future studies targeting the OG, a valuable 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. We have started to develop better protocols in 3-T MRI to depict the OG in living humans (Figure 18) and are applying for funding to depict the OG in 7-Tesla in living humans. The development of an OG-animal model could also be important.

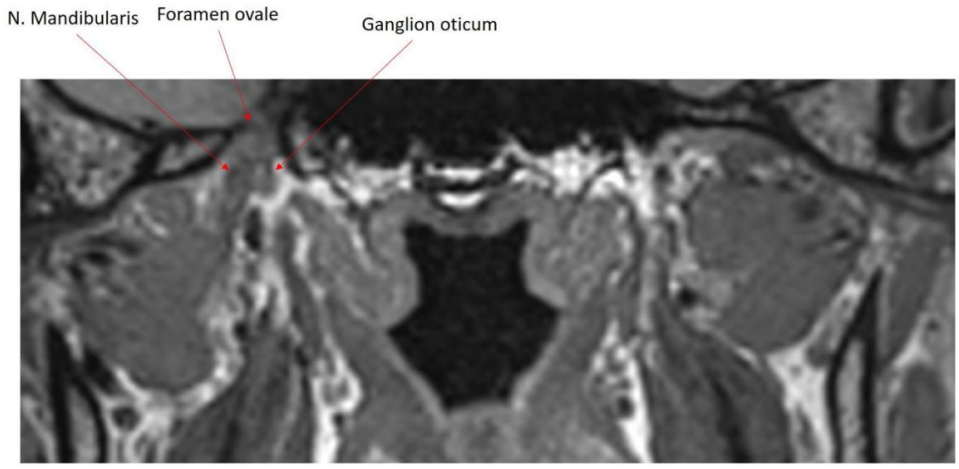


Figure 18: Coronal image obtained in a 3-Tesla MRI scanner. Courtesy of Prof. Erik Magnus Berntsen.

*Utopia for realists in headache disorders*

Headache disorders continue to be a major under-recognized, underdiagnosed and undertreated problem (8). Through history, different civilizations have dreamed of a better world. For the first time in history, it would appear that most people in wealthy countries believe that children will be worse off than their parents (159, 160). Oscar Wild wrote: "*A map of the world that does not include Utopia is not worth even glancing at, for it leaves out the one country at which Humanity is always landing. And when Humanity lands there, it looks out, and, seeing a better country, sets sail. Progress is the realization of Utopias* (160)." Many neurologists and headache specialists might have dreamed of a headache-free world, but this "utopia" has not yet been sufficiently described. The closest description could be the "Vancouver Declaration on Global Headache Patient Advocacy" published in 2018 and 2019 by Dodick *et al* (161, 162). The Vancouver declaration has tried to bring focus into headache patient advocacy. Collaboration with local and international patient organizations will be pivotal in order to develop effective treatment strategies (161, 162). The travel towards this "utopia", where headache is no longer a problem for human beings, will require several stages. Better education on headaches for medical students and trainees will be essential to begin the journey. A study published in 2019 by Kristoffersen E. S. *et al.* examining the prestige of different neurological disorders among future neurologists in Norway found that Headache was amongst the disorders with lowest status (163). Another study by Kristoffersen E. S. *et al.* also published in 2019 examining Neurology residents' knowledge of headache management found that knowledge was only moderate at best (164). Many patients worldwide still do not have access to triptans, drugs developed more than 20 years ago (8). Accessibility to established and evidence-based knowledge and implementation of treatments worldwide should become universal. A deeper understanding of the pathophysiology of primary and secondary headaches is needed. Currently there are no curative treatments for TN, CH or other primary headaches. In our desired utopia, we would have curative treatments with no side effects and the use of acute and prophylactic drugs could become part of medical history books.

*Sustainable research and treatment for headache disorders*

This Thesis aims to be a small step towards a pain-free world. However, this aim is meaningless if we do not have a world where we can live. Human-made activities disrupt more and more ecosystems (165). Climate change is putting future generations at risk and might constitute the biggest challenge our generation is facing (166). All our efforts to understand the pathophysiology of conditions such as TN or CH and improve the treatment of our patients will be futile if we do not do this in a more sustainable manner. Little or no focus has been paid to conducting trials in a more sustainable way (167). The carbon footprint of the whole process of conducting a PhD-Thesis has not been studied. In none of the steps of this Thesis, environmental concerns have been taken into account. Under an average PhD program, students attend several international conferences that include air travel. As an example, the International Headache Society 18$^{th}$ Congress in 2017 was held in Vancouver. A roundtrip from Trondheim to Vancouver in economy class produces 1060.9 Kg of $C0_2$ (168). In order to achieve the goal of limiting global temperature rise to below 2° in the 21st century, the estimated maximum emission per person and year would be 1610 kg $CO_2$ (169), only around 600 Kg more than the emissions produced because of that single trip to Vancouver (one of several international conferences attended through this PhD-Thesis). A call for regulating air travel for research purposes has been done (170). Calculating the full carbon-print of a PhD Thesis is beyond the scope of this Thesis, but this problem should be further assessed. Only essential travels for research purposes should be undertaken. More International conferences are being streamed online and this positive phenomenon is accelerating under the current COVID-19 pandemic. Academic boards assessing PhD-projects should consider carbon-footprint of research projects more thoroughly. Ethical committees should demand researchers to include carbon-print calculations in their protocols. Researchers should be stimulated to implement measures that improve their projects from an ecological perspective. Ethical committees demand accurate information about the possible risks and benefits of a treatment but the possible side effects of the environmental consequences of the research project are currently not being evaluated. Several measures should have been considered in order to reduce the negative environmental impacts of this Thesis.

# 12 **Conclusions**

- In paper 1, we found that the SPG's localization can be predicted on CT-images in a series of 21 patients using bony landmarks. The centre of the anterior opening of the VC and a point on the sphenoidal bone (the S-point, red point in Figure 3, paper 1) appear to be reliable anatomical landmarks to predict the SPG position in CT-scans. Targeting the SPG has become more common and several randomized controlled trials utilizing a variety of treatment modalities are ongoing. Most of the groups who target the SPG do not localize it directly and rely in old unvalidated anatomical landmarks. To accurately predict the location of the SPG on CT-scans will be important both in clinical trials and in clinical practice for those who choose CT-guided techniques. Being able to localize the SPG without the use of MRI will be valuable for those investigators and patients with limited access to MRI, for those patients with contraindications for an MRI and in those where repeated injections are needed. Further studies to validate this method in larger groups of patients are warranted.

- In paper 2, the injection of 25 U of onabotulinum toxin A towards the SPG in 10 patients with classical TN (ICHD-3 beta criteria) appeared to be safe. No severe AEs were observed. A total of 13 AEs were observed in 6 patients. The most frequent side effects were jaw problems and pain or swelling at the injection side (all these AEs remitted within less than 4 weeks after treatment. The study presented in paper 2 does not give any indication for effect in reducing the number of TN attacks after injection of 25 U of BTA towards the ipsilateral SPG. There were 4 patients who were treatment responders, with at least 50% reduction in the median number of attacks between baseline and weeks 5-8, and 2 patients had complete remission of pain after injection with BTA towards the SPG. In this study, intensity of attacks was reduced at weeks 5-8 compared to baseline. Persistent concomitant pain was also reduced after injection. We cannot exclude the possibility of this positive effects being a consequence of

placebo effect (especially in the setting of a surgical trial), regression to the mean or natural fluctuation of the disease. Some positive findings in this study might warrant future RCTs examining whether an SPG block could be effective in patients with classical and idiopathic TN (ICHD-3 criteria). The validation of SPG-block biomarkers should precede further RCTs. International guidelines for conducting controlled trials should clarify whether intensity of pain might be a better primary efficacy outcome than number of attacks.

- In paper 3, the mean distance from the inferior aspect of the foramen ovale to the OG, measured in 15 infratemporal fossae from high definition photographs of anatomical preparations, was 4.5 mm (SD 1.7), range 2.1 – 7.7 mm. These measurements should be validated in a bigger sample, ideally not in photographs of cadaveric preparations (i.e. either directly in anatomical specimens or preferably in living human beings using improved MRI sequences to depict the OG). This distance might be of help when trying to develop navigation-based therapies targeting the OG in future studies.

- In paper 4, the injection of 12.5 or 25 U of onabotulinumtoxin A towards the OG in 10 patients with intractable chronic CH appears to be safe. No severe AEs were observed and all AEs were considered to be mild and had disappeared by the end of the follow-up period of 6 months. Seventeen AEs were observed in 6 of the 10 patients and all AEs had resolved by the end of the follow up period. The most common AEs were pain or swelling at the injection side in 3 patients (which resolved within the first month after injection) and dry mouth also in 3 patients (this symptom resolved within 1 month, by month 3 and by month 6 after injection respectively). We cannot be sure that the study drug entered the OG since the OG was not localized directly. We did not find a clear indication that further placebo-controlled trials injecting BTA towards the OG are warranted. A better description of the topography of the OG in living humans should precede further clinical studies targeting this structure. Future research is needed to establish the role of the OG in headache disorders.

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# 14 Appendix

## Paper 1

**Prediction of the sphenopalatine ganglion localization in CT-images**

## Paper 2

**Pilot Study of Injection of OnabotulinumtoxinA Toward the Sphenopalatine Ganglion for the Treatment of Classical Trigeminal Neuralgia**

## Paper 3

**Anatomical landmarks for localizing the otic ganglion, a possible new treatment target for headache disorders**

## Paper 4

**Open-label, multi-dose, pilot safety study of injection of onabotulinumtoxinA towards the otic ganglion for the treatment of intractable chronic cluster headache**

# Paper I

*Article*

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# Prediction of the sphenopalatine ganglion localization in computerized tomography images

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## Abstract

**Background:** The sphenopalatine ganglion (SPG) is a target for several headache syndromes. Most of the groups targeting the SPG do not localize it directly, and this might account for some therapeutic failures. As the SPG cannot be seen on computerized tomography (CT) scans, magnetic resonance image (MRI) must be used to visualize the ganglion. It would be advantageous to be able to predict the location of the SPG on CT scans for those using fluoroscopy or CT-guided injections and for those in whom MRI is not accessible or contraindicated.

**Methods:** We localized the SPG in 21 Caucasian patients (21 right and 17 left ganglia; total 38) in 3 tesla MR images subsequently fused with CT scans. We measured the distance from the SPG to two bony landmarks identified on CT scans. We then applied the average distances to find an estimated position of the SPG. The first landmark was the center of the anterior opening of the vidian canal (VC). The second landmark was a point on the sphenoidal bone, defined in an axial plane at the level of the center of the VC (S-point). The predicted position of the SPG measured from the VC and the sphenoidal bone were referred to as, respectively, vcSPG and sSPG. Finally, the distances between the SPG, as seen on MRI, and predicted vcSPG/sSPG were calculated.

**Results:** The average distance between SPG as seen on the MRI images and the estimated position based on CT images were 1.82 mm (SD 0.83, range 0.22–3.57 mm) for vcSPG and 2.09 mm (SD 0.99, range 0.71–4.79 mm) for sSPG.

**Conclusions:** The localization of the SPG can be predicted on CT images using bony landmarks. Localization of the SPG may be important in achieving successful therapeutic outcomes for treatments that are directed toward the SPG.

## Keywords

CT scan and MRIs, headache, pterygopalatine ganglion, sphenopalatine ganglion, SPG

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## Introduction

The sphenopalatine ganglion (SPG) is the target for the treatment of several headache conditions.[1] The SPG is situated in the sphenopalatine fossa, which is a complex anatomical region deep in the face behind the maxillary sinus. The SPG cannot be visualized on fluoroscopic or computerized tomography (CT) images due to its tissue properties and size. This makes it a challenge to target the SPG (Figure 1), and most of the techniques targeting this structure are performed without knowing its exact position (Table 1).[24] Some authors have used fluoroscopic guidance or CT-guided techniques, but the anatomical landmarks are not properly validated or standardized. Bratbak et al. have localized the SPG in magnetic resonance imaging (MRI) images in living humans for the first time[25] and used the exact localization of the SPG in a novel technique in two pilot studies.[2,3]

Access to MRI is limited in many countries,[26] and some patients cannot be examined with MRI due to metallic implants,[27] foreign bodies,[28] or claustrophobia.[29] Furthermore, CT scans are more accessible both in number and in cost than MRI. Thus, it would be highly valuable to be able to predict the localization of the SPG using CT scans.

In this study, we evaluate two different methods for predicting the position of SPG on CT scans by measuring the distance in three planes between the SPG and two different landmarks and calculating the distance between the known position as identified on MRI and the predicted position for the two methods.

## Methods

Written informed consent was obtained from all patients. All patients were recruited from four clinical trials approved by the Central Norwegian Regional Ethical Committee (ref. 2012/164, 2014/962, 2015/1193, and 2015/2018) and registered at ClinicalTrial.gov (NCT02019017, NCT02259075, NCT02662972, and NCT02784262). None of the patients had previously had any invasive procedure toward the SPG.

All 27 patients included in clinical studies targeting the SPG at St Olavs University Hospital from 2013 to 2017 were screened. MRI and CT scans had been performed on all patients to enable the study treatment, MRI was performed according the protocol as described by Bratbak et al.[25] for identification of the SPG. The MRI scans were assessed independently by two observers. To avoid the introduction of errors, only sides where both observers were positively certain of the position of the SPG were included. All measurements were done by JCV and DB, and in case of discrepancies, average values were used.

We first localized the SPG on 3 tesla MRI scans in 38 sides. MRIs were fused with CT images using Brainlab iPlan 3.0 (Brainlab AG, Feldkirchen, Germany). Correct co-registration was controlled visually by two physicians (JCV and DB). MRIs and CT scans were obtained on the same day and in all cases prior to intervention. The coordinates of the center of the SPG on an axial plan and two bony landmarks were calculated using Brainlab iPlan 3.0. We used the coordinates to measure the distance in three planes from the center of the SPG to two different bony landmarks identified on CT scans for each participant. We then applied the average distances of the cohort to find an estimated position of the SPG for each participant. The coordinates of the estimated and the real position of the SPG were used to calculate the absolute distance between the two positions using a free online 3-D Calculator Resource.[30] The chosen landmarks were the vidian canal (VC) and the sphenoidal bone. The VC was defined as the center of the anterior opening of the canal using both axial and sagittal CT images through the VC (Figure 2), and the predicted position of the SPG according to this method was referred to as vcSPG. The second landmark was a point on the sphenoidal bone (the S-point), which was defined in an axial plane at the level of the center of the VC as depicted in Figure 3. First, a line parallel to the sagittal plane was drawn (pink line in Figure 3), second, a line with an angle of 45° to the sagittal plane positioned as a tangent on the curvature of the sphenoidal bone laterally to the VC was drawn (cyan line in Figure 3), and the point of contact with the cortex of the sphenoidal bone was registered as the S-point (red point in Figure 3). Bratbak et al. have described the average distance from the center of the SPG to the nearest point of the posterior limitation of the sphenopalatine fossa in the same data set to be 1.6 mm.[25] Based on our measurements in this study, the SPG was depicted 1.0 mm inferior to the axial plane of the opening of the VC. According to these findings, the predicted position of the SPG according to this method was referred to as sSPG (green point in Figure 3) situated 1.6 mm from the S-point on the discontinuous yellow line (perpendicular to the cyan line) and 1.0 mm inferior to the S-point.

MR scans were performed on a 3-tesla scanner (Siemens' Magnetom Skyra, Germany). Technical parameters were as follows: sagittal T2 weighted: repetition time (TR) range 3780, echo time (TE) 111, slice thickness 2 mm, matrix $0.4 \times 0.4 \times 2.0$ mm$^3$, field of view (FOV) 210, number of acquisitions 3; sagittal T1 weighted: TR range 710, TE 10, slice thickness 2 mm, matrix $0.4 \times 0.4 \times 2.0$ mm$^3$, FOV 210, number of acquisitions 2; axial T2 weighted: TR range 4160, TE 110, slice thickness 2 mm, matrix $0.4 \times 0.4 \times 2.0$ mm$^3$, FOV 220, number of acquisitions 2; and axial T1 weighted: TR range 710, TE 7.9, slice thickness 2 mm, matrix $0.4 \times 0.4 \times 2.0$ mm$^3$, FOV 210, number of acquisitions 2. All CT scans were performed using a helical CT scanner (Siemens' Somatom sensation 64, Germany) set at effective mAs 63, 120 kV, slice thickness 1 mm, reconstruction increment 0.7 mm, collimation $12 \times 0.6$ mm$^2$, Kernel U 70, window width 1750.0 HU and window level 450.0 HU.

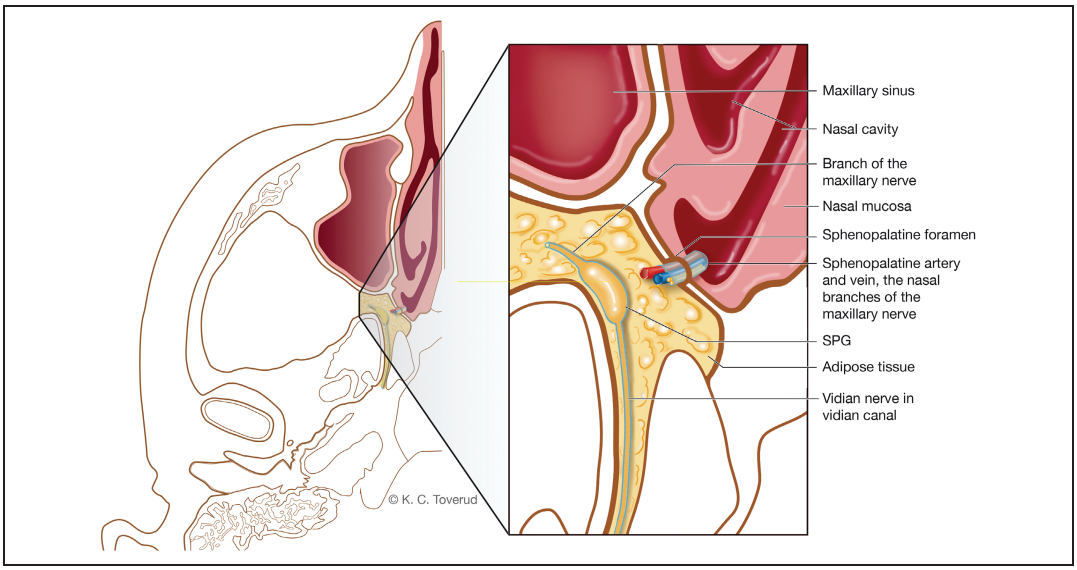


**Figure 1.** Illustration showing the anatomical structures surrounding the SPG in an axial plane. SPG: sphenopalatine ganglion.

**Table 1.** Technique used to localize the sphenopalatine ganglion in different studies that have targeted it.

| Technique | Localization of the SPG | Interventional imaging technique | References |
|---|---|---|---|
| PRF and RFTA | Indirectly (bony landmarks) | Fluoroscopy or CT guided | 4,9–19 |
| Alcohol injection | No | — | 20–22 |
| | Indirectly (bony landmarks) | Fluoroscopy or CT guided | 5–7 |
| Neurostimulation | Indirectly (bony landmarks) | CT or CBCT preoperative<br>Fluoroscopy intraoperative | 8,23 |
| Botulinum toxin | Direct identification of the SPG on MRI | Fused MR and CT images | 2,3 |

CBCT: cone beam computerized tomography; CT: computerized tomography; MR: magnetic resonance; SPG: sphenopalatine ganglion; PRF: pulsed radiofrequency; RFTA: radiofrequency thermoablation.

### *Statistical analysis*

SPSS version 24.0 (SPSS Inc., Chicago, Illinois, USA) was used in the data analyses. Data distributions are expressed as means and standard deviations (SDs). Results are given as mean $\pm$ SD if not otherwise stated.

## Results

The demographics of the sample are described in Table 2. Both investigators were positively certain of the position of the SPG on MRI in a total of 38 sides (21 right and 17 left SPG) in 21 patients (Figure 4). A total of 16 sides were rejected due to uncertainty of position among both investigators. The average distances from bony landmarks to the SPG are depicted in Table 3. The average distance between the SPG, as located in MRI images, and the estimated position based on measurements from the VC (vcSPG) and the sphenoidal bone (sSPG) was, respectively, 1.82 mm (SD 0.83; range 0.22–3.57 mm) and 2.09 mm (SD 0.99; range 0.71–4.79 mm).

No statistically significant differences were observed between genders or side regarding the average distance between the SPG and the estimated SPG (an independent-samples Mann–Whitney *U* Test was used for this purpose).

## Discussion

In this study, we show that the localization of the SPG can be predicted on CT images using bony landmarks. The center of the anterior opening of the VC and the point on the cortical aspect of the sphenoidal bone (described as S-point in this article; red point in Figure 3) appear to be reliable anatomical landmarks to predict the position of the SPG. In this study, we find that the VC is more accurate than the S-point when one tries to predict the localization of the SPG with a more favorable mean distance (1.82 mm vs. 2.09 mm, respectively) and a narrower range (0.22–3.57

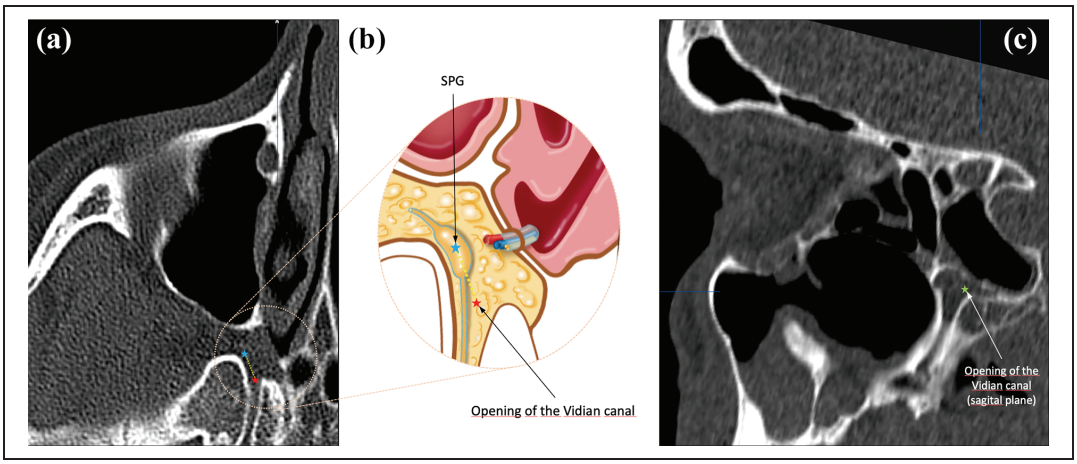


**Figure 2.** (a) Axial CT scan through the opening of the VC(red star); the blue star shows the localization of the SPG previously localized in fused MRIs. The distance between the opening of the VC and the SPG was measured using Brainlab iPlan 3.0 (represented with a yellow discontinued line). (b) Illustration showing an enlarged detail of the image on the left. (c) Parasagittal CT scan through the opening of the VC (green star). SPG: sphenopalatine ganglion; VC: vidian canal; CT: computed tomography.

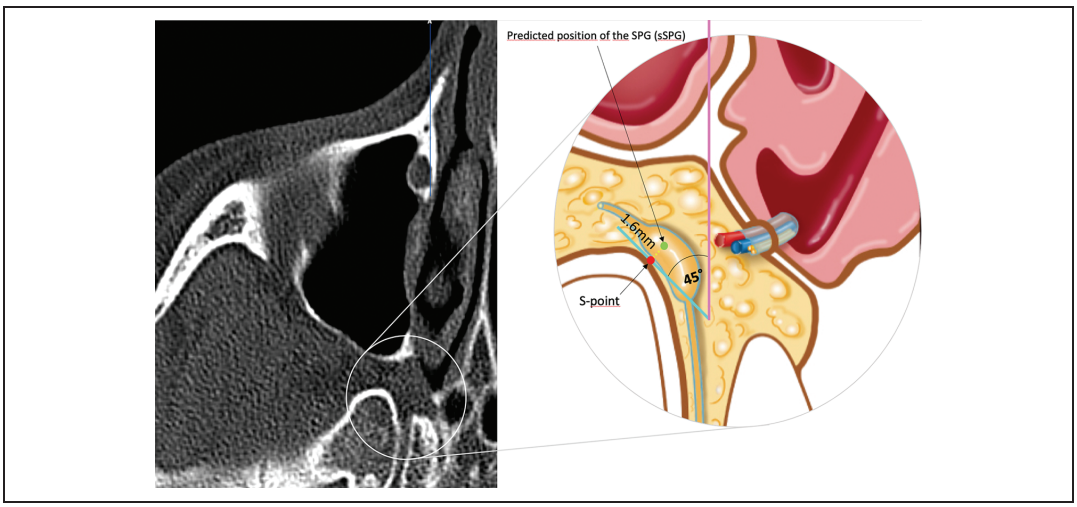


**Figure 3.** Axial CT scan through the opening of the VC (enlarged detail on the right). A line parallel to the sagittal plane is drawn (pink line). Then a line with an angle of 45° to the sagittal plane is positioned as a tangent on the curvature of the sphenoidal bone laterally to the VC (cyan line), and the point of contact with the cortex of the sphenoidal bone is registered as the S-point (red point). The predicted position of the SPG (green point, referred in this article as sSPG) was 1.6 mm from the S-point on the discontinuous yellow line (perpendicular to the cyan line) and 1.0 mm inferior to the S-point. SPG: sphenopalatine ganglion; VC: vidian canal; CT: computerized tomography.

mm vs. 0.71–4.79 mm). This might be because the opening of the VC is a more constant anatomical landmark.

Even though the SPG has been the target for treating headache for more than a century,[31] it has regained interest in the last decade with the development of several novel interventions. Most of these interventions do not localize the SPG and only recently has the SPG been identified in living humans on MRI [25] and exploited with the aim of increasing accuracy when targeting the SPG.[2,3] Most of the authors targeting the SPG rely on cadaveric descriptions where the SPG has been assumed to lie in the sphenopalatine fossa right under the sphenopalatine foramen.[31] However, these descriptions are vague and the location of the SPG in cadaveric studies might be different

**Table 2.** Demographics and clinical characteristics of the sample.

| | |
|---|---|
| Number of screened patients | 27 |
| Number of included patients | 21 |
| Number of females/males | 14/7 |
| Number of included sides (ganglia) | 38 |
| Age (years), mean ± SD (range) | 49 ± 13 (26–70) |
| Number of Caucasians | 21/21 |
| Primary condition | |
| • Chronic cluster headache | 8/21 |
| • Chronic migraine | 8/21 |
| • Trigeminal neuralgia | 2/21 |
| • Nasal polyposis | 3/21 |

SD: standard deviation.

than its location in vivo as a result of postmortem desiccation.[24]

The ability to accurately predict the location of the SPG on CT scans, based on validated anatomical landmarks in vivo, would be highly advantageous for those using CT-guided techniques. This should optimize the accurate delivery of the treatment and optimize patient outcomes. Fewer side effects may also be expected if correction(s) of the position of the needle during the procedure is avoided. Even though the SPG cannot be identified on CT scans, our results show that the localization of the ganglion can be accurately predicted. Being able to use CT images instead of MRI would make it easier to target the SPG in locations with limited access to MRI[26] or in patients who have contraindications to MRI.[27–29]

Depending on the therapeutic strategy, different levels of precision might be acceptable when predicting the localization of the SPG. For instance, using the methods described in this article, an error of 1.82 mm (SD 0.83, range 0.22–3.57 mm) or 2.09 mm (SD 0.99, 0.71–4.79 mm) might be acceptable for most injected drugs, because these distances will probably be overcome by the diffusion of the drug.

All studies using pulsed radiofrequency (PRF) and radiofrequency thermal ablation (RFTA), as depicted in Table 1, have used either fluoroscopy or CT-guided punctures to place the tip of the needle toward the SPG. It has been described that the correct placement of the needle can be achieved by stimulation, as the stimulation of the SPG produces paresthesia in the root of the nose.[4] This does not need to be due to the correct placement of the needle at the SPG, because stimulation anywhere along the posterior lateral nasal nerves on its course from the SPG to the sphenopalatine foramen would elicit paresthesia in the same region. In addition, the technique depends on the patient's subjective sensory perception and has never been validated. One can speculate that treatments using PRF or RFTA would be optimized using navigation toward the SPG with validated anatomical landmarks, achieving better results and reducing the risk for complications.

Other groups have injected various substances such as alcohol toward the SPG using CT-guided techniques.[5–7] The anatomical landmarks used by these groups have not been validated. Whether CT-guided interventions toward the SPG are more effective and safer than other techniques should be evaluated in a randomized controlled trial.

In a publication describing a technique to implant a stimulator targeting the SPG,[8] the authors claim that the

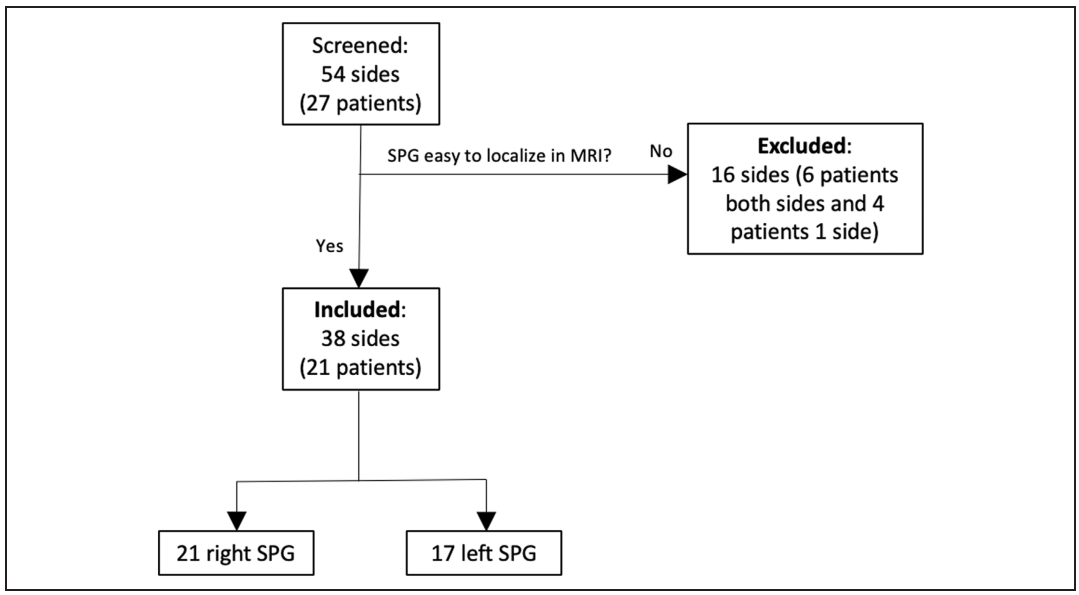


**Figure 4.** Patients included in the study. SPG: sphenopalatine ganglion.

**Table 3.** Average distances ± SD from bony landmarks to the pterygopalatine ganglion (SPG) in all three planes.

| | *X* | *Y* | *Z* |
|---|---|---|---|
| Position of the SPG in relation to the center of the anterior opening of the VC | 2.9 mm (lateral) ± 1.2 | 3.8 mm (anterior) ± 1.2 | 1.0 mm (inferior) ± 1.0 |
| Position of the SPG in relation to the S-point on the sphenoidal bone (red point in Figure 3) | 0.9 mm (medial) ± 0.5 | 1.4 mm (anterior) ± +0.4 | 0.2 mm (inferior) ± +0.2 |

VC: vidian canal. *X*: lateromedial; *Y*: craniocaudal; *Z*: anterioposterior; SPG: sphenopalatine ganglion.

putative location of the SPG is "typically located posterior to the middle nasal turbinate, between the VC and the foramen rotundum." This assumed topography has not been validated in vivo. Whether the use of the proposed anatomical landmarks in this study would increase the precision when inserting such stimulators toward the SPG may deserve further investigations.

### *Limitations of the study*

All 21 patients in this study are White Caucasians, and this may constitute a limitation when extrapolating to other populations. On the other hand, it favors the homogeneity of the sample for internal analysis. Thirty percent of the sides were rejected, and 22% of the patients could not be assessed because of inability to come to consensus on the location/visualization of the SPG.

Another limitation of the study is the female predominance of the sample (14 females vs. 7 males), although no statistically significant differences were observed between genders regarding the average distance between the SPG and the estimated SPG.

The method of identification of the SPG on MRI has only been studied by our group[25] and has not been validated by others.

CT scans have a clear disadvantage compared to MRIs, that is, radiation of the patient. Nonetheless, the use of navigation-based approaches allows for repeated interventions without the need for fluoroscopy under each treatment. Moreover, a baseline CT scan can be used for consecutive treatments, thus reducing considerably the total amount of radiation.

In some patients, the SPG does not appear as a single macroscopic structure,[32] and this might be a limitation when using the methodology to localize the SPG described in this study or when using any other method that does not localize directly the SPG.

## Conclusion

The localization of the SPG can be predicted on CT images using bony landmarks. The center of the anterior opening of the VC and the S-point (red point in Figure 3) appear to be reliable anatomical landmarks to predict the position of the SPG. Targeting the SPG has become more common and several randomized controlled trials utilizing a variety of treatment modalities are ongoing. To accurately predict the location of the SPG on CT scans will be important both in clinical trials and in clinical practice for those who choose CT-guided techniques. Being able to localize the SPG without the use of MRI will be valuable for those investigators and patients with limited access to MRI, for those patients with contraindications for an MRI and in those where repeated injections are needed. Further studies to validate this method in larger groups of patients are warranted.

### Author contributions

JC, DB, and ET had the original idea for the manuscript. JC and DB analyzed the data. JC reviewed the literature for the introduction and discussion and drafted the manuscript. DB, DD, MM, KJ, and ET provided assistance for drafting the manuscript and revision of the text. All authors read and approved the final manuscript.

### Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The results of this study may affect opinions on the feasibility of interventional treatments targeting the SPG. An intervention device for image-guided injections of pharmacological substances towards the SPG is developed at NTNU and St. Olavs Hospital, Trondheim University Hospital. These institutions may benefit financially of a commercialization of the device through future possible intellectual properties, this may include financial benefits to authors of this article. Dr Bratbak is co-inventor of a proposed treatment targeting the SPG and the intervention device used to perform the treatment, both inventions patent pending, and may benefit financially of a commercialization of the proposed treatment through future possible intellectual properties. Dr Tronvik may benefit financially of a commercialization of a proposed treatment targeting the SPG and the intervention device used to perform the treatment through future possible intellectual properties. Within the last 12 months, Dr Dodick reports personal fees from Amgen, Alder, Allergan, Autonomic Technologies, Biohaven, Eli Lilly, eNeura, Foresight Capital, Neurolief, Zosano, WL Gore, Vedanta Associates, Promius Pharma, Nocira, Novartis, Electrocore, Teva, Ipsen, Impel, Satsuma, Theranica. Compensation for activities related to data safety monitoring committee from Axsome. Compensation related to CME content development: Healthlogix, Medicom Worldwide, Medlogix Communications, MedNet, Miller Medical Communications, PeerView Operation Services America, Web MD/Medscape, American Academy of Neurology, American Headache Society, PeerView Institute for Medical Education, Chameleon Communications, Academy for Continued Healthcare Learning, Universal Meeting

Management, Haymarket Medical Education, Global Scientific Communications, UpToDate, Meeting LogiX. Royalties from editorial or book publishing: Oxford University Press, Cambridge University Press, Wiley Blackwell, Sage, Wolters Kluwer Health. Consulting use agreement through employer: NeuroAssessment Systems, Myndshft. Equity (stock options): Aural Analytics, Healint, Theranica, Second Opinion/Mobile Health, Epien, Ontologics. Board of Directors position: King-Devick Technologies, Epien, Ontologics. Dr Crespi, Dr Jamtøy and Dr Matharu have no conflicts of interest.

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# Paper II

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# Research Submission

## Pilot Study of Injection of OnabotulinumtoxinA Toward the Sphenopalatine Ganglion for the Treatment of Classical Trigeminal Neuralgia

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**Background.—The sphenopalatine ganglion (SPG) has previously been targeted in trigeminal neuralgia (TN), but its role in this condition has not been established.**

**Objective.—To investigate the safety of injecting onabotulinumtoxinA (BTA) toward the SPG using the MultiGuide® in 10 patients with refractory classical TN, and collect preliminary efficacy data.**

**Methods.—Twenty-five international units (IU) of BTA were injected toward the SPG in a prospective, open-label study in 10 patients with refractory classical TN. All patients were recruited and treated on an out-patient basis at St. Olav's University Hospital in Trondheim (Norway). Primary outcome: adverse events (AEs). Primary efficacy outcome: number of TN attacks at weeks 5-8 after injection compared to baseline. A treatment responder was predefined as at least 50% reduction in the median number of attacks per day between baseline and weeks 5-8. Other efficacy outcomes were intensity of attacks (numeric rating scale, 0 to 10) and functional level (1 to 4; 1 best and 4 worst) at weeks 5-8 after injection compared to baseline. Percentage of the day with concomitant persistent pain was registered at baseline and at weeks 1-4, 6, 8, and 12 after injection. Patient global impression of change (PGIC) was ascertained at month 3.**

**Results.—For the primary endpoint, we analyzed data for all 10 patients. For efficacy outcomes we analyzed data for 9 patients (1 patient violated protocol). We registered 13 AEs, none of which were serious. The median number of TN attacks during the 4-week baseline and weeks 5-8 after injection was 5.5 (range: 1.0-51.5) and 5 (range: 0-225.0), respectively ($P$ = .401). Four patients were treatment responders. The median intensity of attacks at baseline and weeks 5-8 after injection was 6 (range: 3.0-8.5) and 3 (range: 0.0-9.0) respectively ($P$ = .024). The median functional level at baseline was 2 (range: 1.0-3.3) and at month 2, 1 (range 1.0-4.0; $P$ = .750). Median percentage of the day with concomitant persistent pain was 75% (minimum 37.5%, maximum 100%) at baseline and 18.75% (minimum 0%, maximum 100%) at week 8 ($P$ = .023).**

**Conclusions.—Injection of BTA toward the SPG using the MultiGuide® in patients with TN appears to be safe and well tolerated. This study was negative for the main efficacy endpoint (reduction in the number of attacks from baseline to weeks 5-8). Further studies examining the role of the SPG in TN are necessary.**

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**Key words: trigeminal neuralgia, sphenopalatine ganglion, pterygopalatine ganglion, botulinum toxin, sensitization**

**Abbreviations: CT computerized tomography, MRI magnetic resonance imaging, SD standard deviation, SPG sphenopalatine ganglion, TN trigeminal neuralgia**

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## INTRODUCTION

Classical trigeminal neuralgia (TN) is defined as recurrent paroxysms of unilateral facial pain.[1] The etiology of classical TN has been researched extensively, but the exact pathophysiological processes leading to pain are not fully understood. Central to the pathogenesis seems to be a neurovascular contact,[2] but there is also evidence of the involvement of central pain mechanisms.[3,4] Patients with TN often have a refractory period and this well-documented clinical feature suggests a central mechanism.[3,5]

In a prospective series of 158 patients with classical TN, 31% had autonomic symptoms.[6] These symptoms included conjunctival injection and tearing, rhinorrhea, and nasal congestion.[6] These symptoms may reflect activation of cranial parasympathetic efferents from the sphenopalatine ganglion (SPG).[7,8]

The SPG may be involved in pain sensitization and it has been suggested that parasympathetic outflow contributes to pain by activating or sensitizing intracranial nociceptors.[9] In the same series of 158 patients with TN cited above, it was observed that 78 patients (49%) had concomitant persistent pain.[6] Central facilitation of trigeminal nociceptive processing has been described in patients with TN with concomitant persistent facial pain.[4]

Treatment of TN includes both pharmacological and surgical treatments.[10] The role of the SPG in the pathogenesis of TN is not clear and high-quality randomized controlled trials (RCTs) have not been performed. Studies attempting to block the SPG in TN have been summarized in the literature.[11,12] The overall grade of recommendation for SPG block in TN is grade B.[11] In the only RCT conducted in TN attempting to block the SPG, 25 patients were randomized to be treated with either intranasal lidocaine 8% or placebo for second-division TN.[13] The lidocaine group had prompt but temporary analgesia. It should be noted that intranasal injection of drugs has not been proven to achieve blockade of the SPG and that proper blinding of intranasal local anesthetics may not have been achieved.[14] Other authors have also targeted the SPG in TN with varying results.[15-22]

Parasympathetic fibers synapse in the SPG using acetylcholine as neurotransmitter.[7] onabotulinumtoxinA (BTA) blocks the release of acetylcholine and 2 pilot trials have examined the safety of injections of BTA toward the SPG in patients with intractable

*Conflict of Interest:* Dr. Bratbak is co-inventor of the device used to perform the treatment (patent pending) and may benefit financially from the commercialization of the device. Dr. Tronvik may benefit financially of a commercialization of a proposed treatment targeting the SPG and the intervention device used to perform the treatment through future possible intellectual properties. Within the last 12 months, Dr. Dodick reports personal fees from Amgen, Alder, Allergan, Autonomic Technologies, Biohaven, Eli Lilly, eNeura, Foresight Capital, Neurolief, Zosano, WL Gore, Vedanta Associates, Promius Pharma, Nocira, Novartis, Electrocore, Teva, Ipsen, Impel, Satsuma, Theranica. Compensation for activities related to data safety monitoring committee from Axsome. Compensation related to CME content development: Healthlogix, Medicom Worldwide, Medlogix Communications, MedNet, Miller Medical Communications, PeerView Operation Services America, Web MD/Medscape, American Academy of Neurology, American Headache Society, PeerView Institute for Medical Education, Chameleon Communications, Academy for Continued Healthcare Learning, Universal Meeting Management, Haymarket Medical Education, Global Scientific Communications, UpToDate, Meeting LogiX. Royalties from editorial or book publishing: Oxford University Press, Cambridge University Press, Wiley Blackwell, Sage, Wolters Kluwer Health. Consulting use agreement through employer: NeuroAssessment Systems, Myndshft. Equity (stock options): Aural Analytics, Healint, Theranica, Second Opinion/Mobile Health, Epien, Ontologics. Board of Directors position: King-Devick Technologies, Epien, Ontologics. Dr. Crespi, Dr. Jamtøy and Dr. Matharu have nothing to disclose.

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chronic cluster headache and intractable chronic migraine.[23,24]

Given the reports suggesting that the SPG may be a viable therapeutic target for trigeminal pain syndromes, including TN, and that blockade of the SPG with BTA may be an effective intervention, we decided to examine the safety of injections with BTA toward the SPG in patients with classical TN using a new navigation device (the MultiGuide®) and to collect pilot data on efficacy to inform and power future potential RCTs.

## METHOD

**Study Design and Participants.—**A total of 10 patients with classical TN (ICDH-3 Beta criteria) were recruited and treated between September 2015 and October 2018 at St. Olav's University Hospital, Trondheim, Norway. There was a baseline registration of 1 month previous to injection and the follow up was 3 months. One study month equaled 28 days.

Table 1 shows inclusion and exclusion criteria.

All 10 patients were examined by a neurologist and CT and MRI scans of the sphenopalatine fossa were obtained before injection. Patients had to keep a daily diary 4 weeks prior to and for 3 months after the injection recording adverse events (AEs), number of TN attacks, intensity (using a numeric rating scale [NRS] from 0 to 10) and functional level ("how much of your planned activities for the day did you manage to complete": 1: all; 2: more than 50%; 3: less than 50%; 4: none). Patients were instructed to count each paroxysm as an attack. The intensity level was recorded as an average of the individual paroxysms through 1 day.

**Description of the Procedure.—**Our research group has developed a novel injection device to perform surgical navigation-assisted administration of BTA toward the SPG (the MultiGuide®, Fig. 1) ipsilateral to the pain. A single treatment was performed on an awake participant, using local anesthesia, in an outpatient office-based setting using a percutaneous, infrazygomatic approach using the MultiGuide®, 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 on awake individuals and it enables repeated treatments without acquiring new CT and/or MRI for better radiation hygiene and lower cost. Pre-treatment planning of CT and MRI was performed with Brainlab iPlan 3.0 (Brainlab AG, Feldkirchen, Germany). The SPG ipsilateral to the pain was localized visually and marked on fused MRI and CT scans. With the patient in a supine

**Table 1.—Inclusion and exclusion criteria**

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| • Willing to sign informed consent<br>• Age 18 to 80<br>• Classic TN according to ICHD-3b<br>• Unsatisfactory effect, intolerable side effects or contraindications of one of the following:<br>  ○ Carbamazepine<br>  ○ Oxcarbazepine<br>And at least one of the following drugs:<br>  ○ Gabapentin<br>  ○ Pregabalin<br>  ○ Baclofen<br>  ○ Lamotrigine<br>  ○ Phenytoin | • Microvascular decompression is considered a better therapeutic choice<br>• Secondary TN<br>• Systemic or local disease that can interfere with the treatment<br>• Bilateral TN<br>• Reduced capacity to give informed consent<br>• Psychiatric condition preventing full participation<br>• Pregnancy or nursing<br>• Inability to use appropriate contraceptives in fertile women<br>• Abuse of drugs, including alcohol<br>• Anatomic anomalies that can hinder or impede treatment<br>• Hypersensitivity to local anesthetics, adrenalin or BTA or concomitant treatment with drugs that might interact with BTA |

BTA = botulinum toxin type A; ICHD-3b = International Classification of Headache Disorders, 3 beta edition; TN = trigeminal neuralgia.

**Fig. 1.—The MultiGuide, a novel injection device to perform surgical navigation-assisted administration of botulinum toxin toward the sphenopalatine ganglion. [Color figure can be viewed at wileyonlinelibrary.com]**

position, the skin and deep structures toward the sphenopalatine fossa were anesthetized with 5-7 ml Marcaine-Adrenalin (5 mg/ml-5 µg/ml, AstraZeneca, Oslo, Norway) and a 1-2mm skin incision was made. Aided by surgical navigation and the MultiGuide®, 25 international units BTA suspended in 0.5 ml isotonic saline was injected toward the SPG ipsilateral to the pain. The estimated duration of the injection is around 3 minutes, and for the whole procedure including navigation system setup 20-30 minutes. In this study, we used the same injection technique as in pilot trials in intractable chronic cluster headache and intractable chronic migraine.[23,24]

**Outcome and Statistical Analysis.—**The primary outcome was occurrence of AEs. All medical complications that participants experienced after the injection during the 3-month follow-up were evaluated as a possible AE. Information for possible AEs was collected from each telephone consultation (at weeks 1-4, 6, and 8 after injection), at last visit (month 3 after injection) and in the headache diaries (each day had a free text box for AEs). All health complaints (also those not requiring further medical intervention) were evaluated as a possible AEs and where in doubt, they were coded as AEs. The main efficacy outcome was number of TN attacks at weeks 5-8 after injection compared to baseline. Efficacy outcomes were measured at weeks 5-8 (predefined in protocol) since onset of efficacy may require up to 4 weeks and maximal benefit would be expected during month 2 prior to the eventual and usual attenuation of the therapeutic effect of BTA during the 3rd month after injection. A treatment responder was predefined as at least 50% reduction in the median number of attacks per day between baseline and weeks 5-8. Other efficacy outcomes were intensity of the attacks, functional level at weeks 5-8 after injection compared to baseline, Patient Global Impression of Change (PGIC) and percentage of the day with concomitant persistent pain.

PGIC was used to record patient's assessment of the change in overall status according to a 7-point NRS (1: very much improved, 2: much improved, 3: minimally improved, 4: no change, 5: minimally worse, 6: much worse, and 7 very much worse) at month 3 after injection.

Patients were asked to record the percentage of the day with concomitant persistent pain at baseline and weeks 1-4, 6, 8, and 12 after injection. The percentage of the day with concomitant persistent pain was stratified as 0%, 1 to 24%, 25 to 49%, 50 to 74%, 75 to 99%, and 100%. A Friedman test (non-parametric

analysis for repeated measurements) was performed. A Wilcoxon rank-sum exact test was used to analyze changes at weeks 1-4, 6, 8, and 12 after injection compared to baseline.

A scale developed to screen for cranial parasympathetic symptoms (CAPS scale[25]) was administered at baseline and 3 months after injection.

For the primary endpoint, we analyzed data for all 10 patients. A protocol violator was defined as a participant with less than 60% of diary days registered or change of prophylactic medication during the study. Missing values were estimated using the last observation carried forward methodology. For efficacy outcomes, we analyzed data for 9 patients (one patient was considered a protocol violator due to failure to count the number of attacks and document their intensity).

The study protocol was approved by the regional ethical committee (REK 2015/1193) and the Norwegian Medicines Agency. All participants signed a written informed consent. This trial received the EUDRACT number: 2015-002643-33 and was registered at ClinicalTrial.gov (NCT02662972).

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. A Friedman test for repeated measurements was performed to analyze changes in the percentage of the day with concomitant persistent pain. Results are given as median and range. Means (±SD) were calculated in order to produce comparable results to other studies targeting the SPG using the same technique.[23,24]

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

## RESULTS

A total of 12 patients were screened. Two patients were considered screening failures during baseline (one due to MRI findings of a brain stem lesion likely causing TN and the other did not feel impacted enough to undergo the study procedure). About 10 patients (3 women and 7 men) completed the study, 1 patient was a protocol violator and efficacy data could not be obtained for this patient. See Table 2 for demographics of the sample.

**Table 2.—Demographics of the Sample**

| Demographics of the sample | |
|---|---|
| Number of screened patients | 12 |
| Number of included patients | 10 |
| Number of females/males | 3/7 |
| Mean age, years ± SD (range) | 59.4 ± 11.77 (39-74) |
| Mean years with trigeminal neuralgia ± SD (range) | 8.3 ± 8.6 (1.5-29) |
| Number of Caucasians | 10/10 |
| Side left/right | 6/4 |
| Hyperesthesia (in the trigeminal territory) | 3/10 |
| Allodynia (in the trigeminal territory) | 2/10 |
| Branches affected | |
| V1 | 7/10 |
| V2 | 10/10 |
| V3 | 9/10 |
| Previous history of stroke | 4/10 |
| Previous history of ischemic heart disease | 2/10 |
| Previous history of hypertension | 3/10 |
| Previous history of depression | 2/10 |

SD = standard deviation; V1 = ophthalmic nerve; V2 = maxillary nerve; V3 = mandibular nerve.

**Table 3.—Drugs Used by the Participants of the Study**

| | Number of Patients (n = 10) | | |
|---|---|---|---|
| Drug | Current Use | Previous Use | Not Tried |
| Carbamazepine | 3 | 5 | 2 |
| Oxcarbazepine | 3 | 2 | 5 |
| Gabapentine | 1 | 9 | 0 |
| Pregabaline | 2 | 3 | 5 |
| Baclofen | 0 | 3 | 7 |
| Lamotrigin | 0 | 1 | 9 |
| Fosphenytoin | 0 | 1 | 9 |

Table 3 summarizes the drugs currently used or previously tried by the 10 patients. The patients had been treated with a mean of 3.3 evidence-based medications (minimum of 2 and maximum of 6 medications) prior to inclusion in this trial.

Three patients had previously undergone microvascular decompression, 1 patient had previously tried glycerol rhizolysis of the trigeminal ganglion, and 1 patient had undergone balloon-compression of the trigeminal ganglion.

**Table 4.—Adverse Events**

| Adverse Events | Number of Patients | | |
|---|---|---|---|
| | Resolved <4 Weeks | Resolved 4-12 Weeks | Resolved Within 4 Months After Injection |
| Pain or swelling | 3 | — | — |
| Jaw problems | 2 | 1 | 1 |
| Nasolabial fold asymmetry | — | — | 2 |
| Diplopia | — | — | 1 |
| Dry eye | — | 1 | — |
| Dysphagia | 1 | — | — |
| Rash | 1 | — | — |

**Primary Outcome (Safety).**—Six out of 10 patients experienced AEs, none were serious (Table 4). All AEs were considered to be mild except for 1 patient who experienced diplopia moderately affecting his daily activities. This was assumed to be due to diffusion of BTA through the inferior orbital fissure which clinically produced a moderate paralysis of the inferior rectus muscle with hypertropia in abduction. The symptoms slowly improved and resolved 1 month after conclusion of the study. This patient had a remarkably narrow sphenopalatine fossa. We believe that this anatomical characteristic played an important role on the development of this AE and this will be taken into consideration for further injections in similar patients.

Two patients experienced mild nasolabial fold asymmetry assumed to have been caused by diffusion of botulinum toxin toward the zygomatic muscles. Both patients reported that the slight asymmetry was not bothersome and resolved within 1 month after the study ended.

One patient experienced mild dysphagia (approximately 2 weeks after injection, it was slightly harder to swallow phlegm, but he did not have dysphagia when drinking or eating). This resolved within 1 month after injection.

Three patients had mild pain or swelling at the injection side that resolved in all cases within the first month after injection. Just 1 of the patients had to take additional analgesics on the day of injection.

Four patients reported mild discomfort in the jaw (ipsilateral to the injection side) at maximal gaping. These jaw problems did not interfere with chewing, eating or speaking and did not require further treatment. Symptoms resolved spontaneously within 1 month after injection in 2 patients, after 3 months in 1 patient, and after 4 months in 1 patient.

One patient experienced mild symptoms of dry eye ipsilateral to the injection. These symptoms appeared 5 weeks after injection and resolved 7 weeks after injection and did not require any treatment.

Of the 13 observed AEs, 7 were considered to be secondary to the procedure (pain or swelling at the injection side and jaw problems) and 5 secondary to BTA (nasolabial fold asymmetry, diplopia, dry eye, and dysphagia). One of the patients developed a mild bilateral facial rash during the study that was not thought to be related to the procedure or the experimental drug.

**Secondary Outcomes (Efficacy).**—For the efficacy outcomes we have analyzed data for 9 patients (excluding the protocol violator with no data available). A 2-sided Wilcoxon Signed Ranks Test was performed to compare the number of attacks, intensity, and function level at baseline and at weeks 5-8 after injection (see Table 5). The median number of attacks per day when comparing baseline vs weeks 5-8 was not statistically significant ($P$ = .401). Four patients were treatment responders with at least 50% reduction in the median number of attacks between baseline and weeks 5-8. Two patients achieved full remission after the injection (patients 5 and 10 in Table 6).

Table 6 shows the median number of attacks and median intensity of attacks at baseline and at weeks 5-8 for each participant.

One can observe that the mean, but not the median, number of attacks per day at weeks 5-8 was increased (Table 5). This was due to an outlier (patient 2 in Table 6), who had a worsening of his TN.

The median intensity of attacks was significantly reduced from baseline (median 6, range 3.0-8.5) vs weeks 5-8 (median 3, range 0.0-9.0; $P$ = .024).

The median function level when comparing baseline vs weeks 5-8 was not statistically significant ($P$ = .750).

**Table 5.—Number of Attacks per Day, Intensity of Attacks Using a Numeric Rating Scale (NRS 0 to 10) and Functional Level ("How Much of Your Planned Activities for the Day did you Manage to Complete": 1: all; 2: more than 50%; 3: less than 50%; 4: none)**

| | | Baseline | Weeks 5-8 | Weeks 5-8 vs Baseline |
|---|---|---|---|---|
| Number of attacks per day | Median (range) | 5.5 (1.0-51.5) | 5.0 (0.0-225.0) | *P* = .401 |
| | Mean ± SD | 11.9 ± 15.6 | 28.3 ± 71.8 | |
| Intensity of attacks | Median (range) | 6.0 (3.0-8.5) | 3.0 (0.0-9.0) | *P* = .024 |
| | Mean ± SD | 5.8 ± 2.1 | 3.65 ± 3 | |
| Functional level | Median (range) | 2.0 (1.0-3.3) | 1.0 (1.0-4.0) | *P* = .750 |
| | Mean ± SD | 1.9 ± 0.81 | 2.0 ± 1.12 | |

SD = standard deviation.

**Table 6.—Median Number of Attacks per day and Median Intensity of Attacks at Baseline and at Weeks 5-8 for Each Participant**

| | Number of Attacks per Day, Median (Range) | | Intensity of Attacks, Median (Range) | | | |
|---|---|---|---|---|---|---|
| Patient | Baseline | Weeks 5-8 | Baseline | Weeks 5-8 | Current Prophylactic Medication | Surgical Interventions Tried |
| 1 | 5.5 (3-10) | 5.0 (3-8) | 6.0 (3-9) | 5.0 (4-8) | Carbamazepine | — |
| 2 | 52.5 (16-90) | 225.0 (25-420) | 8.0 (6-9) | 9.0 (7-9) | Gabapentine | — |
| 3 | 3.0 (2-4) | 2.0 (2-4) | 3.0 (3-5) | 3.0 (2-4) | Pregabaline | — |
| 4 | 2.5 (0-5) | 5.0 (4-10) | 3.5 (0-10) | 2.0 (2-4) | Carbamazepine | Microvascular decompression<br>Glycerol rhizolysis of the trigeminal ganglion |
| 5 | 16.0 (8-40) | 0.0 (0-0) | 8.5 (8-9.5) | 0.0 (0-0) | Paracetamol/codein | — |
| 6 | 13.5 (0-18) | 6 (6-6) | 7.0 (0-8) | 6.0 (6-6) | Oxcarbazepine | — |
| 7 | 15.0 (2-25) | 6.5 (0-113) | 8.5 (6.5-10) | 6.3 (0-10) | Pregabaline | Microvascular decompression<br>Balloon-compression of the trigeminal ganglion |
| 8 | 1.0 (1-1) | 1.0 (0-5) | 4.0 (1-8) | 1.5 (0-5) | Oxcarbazepine | — |
| 9 | † | † | † | † | Carbamazepine | Microvascular decompression |
| 10 | 2.0 (0-4) | 0.0 (0-0) | 4.0 (0-8) | 0.0 (0-0) | Oxcarbazepine | — |

†Patient number 9 was none compliant with the headache diary and was considered a protocol violator.

All patients but 1 had a CAPS scale of 0 (no autonomic parasympathetic symptoms) both at baseline and at month 3 after injection. One patient had 1 point in the CAPS scale before injection due to mild conjunctival injection during attacks (he did not have lacrimation or other symptoms). His CAPS score 3 months after injection was 0. This patient was a responder and went into full remission after treatment.

All patients had persistent concomitant pain at baseline with a median percentage of the day with concomitant persistent pain of 75% (minimum 37.5%, maximum 100%). The Friedman test for repetitive measurements was statistically significant ($P = .031$) indicating reduction in concomitant persistent pain after injection. Concomitant persistent pain at weeks 2 and 8 were significantly lower than

at baseline ($P$ = .027 and $P$ = .023, respectively). These inferences were not statistically significant after proper adjustment for multiplicity. The median percentage of the day with concomitant persistent pain at week 8 was 18.75% (minimum 0%, maximum 100%).

One patient had a PGIC of "very much improved," 2 patients "much improved," 2 patients "minimally improved," 2 "no change," 3 "minimally worse (none "much worse" or "very much worse") after injection.

The pain inflicted upon the patient during the injection was reported on an NRS from 0 to 10 immediately after injection. The mean pain reported was 2 (range 0-2). One out of 10 patients had to use additional analgesics on the day of the injection. Eight out of 10 patients in this study would recommend this treatment to other patients with TN.

## DISCUSSION

In this paper, we have shown that injections of BTA toward the SPG in patients with TN, using a new navigation tool (the MultiGuide®), is safe. No serious AEs were reported in these 10 patients. All AEs remitted at the latest 4 months after the treatment as one would expect with BTA. The main efficacy outcome in this study was negative with median of 5.5 attacks per day in the baseline period vs 5.0 ($P$ = .401) in weeks 5-8. Four patients were treatment responders with at least 50% reduction in the median number of attacks between baseline and weeks 5-8. Two patients had a complete remission after the injection and experienced a recurrence of attacks 1 month after the study end.

Patients with TN who do not have a satisfactory response to pharmacological treatment are often referred for surgical treatment. Quality evidence for efficacy of most neurosurgical procedures for TN has been reported to be very low because of the poor quality of the trials.[26] TN incidence increases with age[27] and affects a population group with high prevalence of comorbidities. Surgical interventions for TN have been reported to be highly effective but they also have a high risk for permanent and severe AEs. Up to 10% of patients undergoing a microvascular compression experience severe perioperative complications.[28] Taha et al have published a review on several percutaneous techniques used in TN and the prevalence of side effects observed in different studies[28,29]). Newer publications examining these techniques have found similar complication rates.[30] Tuleasca et al have summarized the effects of repeat Gamma Knife treatment for TN and found that between 11 and 80% of the patients develop trigeminal hypesthesia.[31] The main concern of the percutaneous techniques are the feared risk of anesthesia of the cornea and anesthesia dolorosa, in addition to high risk of hypoesthesia. These complications are typically permanent while the effect of the treatment is temporary. The risk for side effects in a non-negligible percentage of patients undergoing surgical procedures and the increasing prevalence with age underlines the need for novel, minimally invasive and well tolerated approaches. The AEs of the technique used in this study appears to offer a favorable AE profile with mostly mild and transient AEs and with no severe AEs reported. These results are similar to earlier reports by our group in 2 other pilot trials.[23,24]

The role of the SPG in TN has not been established but several authors have tried to target this structure.[11-13,15-22,32] This study was negative for the main efficacy endpoint (reduction of the number of attacks), but there are several aspects to consider. Four of the 9 subjects were treatment responders. Two patients had a complete remission starting the day following the injection. This remission was sustained for at least 1 month after completion of the study. None of these 2 patients had experienced a similar spontaneous remission previously to the study treatment. In addition, a statistically significant reduction in the intensity of the attacks and concomitant persistent pain was observed. Concomitant persistent pain in patients with TN has not been properly studied nor regarded as an endpoint in clinical trials in TN. ICHD-3 describes a subgroup of classical TN with concomitant continuous or near-continuous pain between attacks in the affected trigeminal distribution.[1] Concomitant persistent pain has been reported in up to 49% of patients with TN.[6] The 2 patients who went into full remission also experienced a complete disappearance of their concomitant persistent pain.

Central pain mechanisms have been invoked in the pathophysiology of TN.[3,4] Lesions induced

in the spinal trigeminal nucleus, but not in the trigeminal ganglion, of cats or rats produce a marked overreaction to tactile stimulation of the face and the occurrence of spontaneous paroxysms of pain also suggesting a central involvement.[3] The refractory period observed in most patients with TN suggests involvement of the central nervous system.[3,5] In patients with TN and concomitant continuous or near-continuous facial pain, central facilitation of trigeminal nociceptive processing, most likely at a supraspinal level, has been demonstrated. This may be an underlying mechanism for development of continuous facial pain due to overactivation of central sensory transmission.[4] The mechanism by which concomitant persistent pain was reduced in this study could either relate to a role of the SPG in pain sensitization,[9] placebo effect, or regression to the mean. Blockade of the SPG may produce a reduction in parasympathetic outflow and thus reduced the activation/sensitization of the intracranial nociceptors and central nociceptive neurons in the spinal trigeminal nucleus, which could theoretically reduce the intensity of attacks and concomitant persistent pain, but not the number of attacks, as observed in this pilot trial. In a series of 158 prospective patients with TN, 48 patients (31%) had autonomic symptoms, the recorded symptoms included conjunctival injection/tearing (22%) and running/clogged nose (16%).[6] All patients but 1 had a CAPS scale of 0 (no autonomic parasympathetic symptoms) during the baseline phase in the present study. The single patient whose CAPS score was reduced to zero 3 months after injection also experienced complete remission of pain. The presence of cranial parasympathetic symptoms may be a marker that predicts response and the low prevalence of patients with cranial parasympathetic symptoms in this study population may have negatively affected the efficacy outcomes.

**Limitations of the Study.—**This was a small open-label study. The placebo response in a previous study were patients with TN were randomized to a multi-point injection (between the epidermis and dermis) of either 25 IU of BTA, 75 IU of BTA or placebo was 32.1%.[33] The reduction of intensity in attacks and reduction in the percentage of the day with concomitant persistent pain observed in this study might have been due to placebo effect. It has also been documented that regression to the mean and periods of remission may bias the results in uncontrolled studies.[34]

## CONCLUSION

Injection of botulinum toxin toward the SPG using the novel MultiGuide® system in patients with TN appears to have an acceptable adverse event profile as has been shown in other studies using the same technique.[23,24]

The main efficacy endpoint in this study (reduction in number of attacks) was negative, but a significant reduction in the intensity of the attacks and concomitant persistent pain was observed. There were 4 patients with at least 50% reduction in the median number of attacks between baseline and weeks 5-8, and 2 patients experienced complete remission of pain after the injection.

This study does not give any indication for effect in reducing the number of TN attacks after injection of 25 IU of BTA toward the SPG. Further studies examining the role of the SPG as a therapeutic target for TN are necessary.

## CLINICAL IMPLICATIONS

- The injection of onabotulinum toxin A toward the SPG in TN appears to be safe.
- This study does not give any indication for effect in reducing the number of TN attacks after injection of 25 IU of BTA toward the SPG.
- There were 4 patients with at least 50% reduction in the median number of attacks between baseline and weeks 5-8, and 2 patients had complete remission of pain after the injection.

## AUTHORS' CONTRIBUTIONS

JC, DB, and ET had the original idea for the manuscript. JC, DB and ET analyzed the data. JC reviewed the literature for the introduction and discussion and drafted the manuscript. DB, DD, MM, KJ, and ET: assistance for drafting the manuscript and revision of the text. All authors read and approved the final manuscript.

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# Paper III

*Original Article*

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# Anatomical landmarks for localizing the otic ganglion: A possible new treatment target for headache disorders

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## Abstract

**Background:** The otic ganglion (OG) is a cranial parasympathetic ganglion located in the infratemporal fossa under the foramen ovale (FO) and adjacent to the medial part of the mandibular nerve. Parasympathetic innervation of intracranial vessels from the OG has been shown both in animal and human models and evidence suggests that the OG plays an important role in the cranial vasomotor response. We review the evidence that positions the OG as a viable target for headache disorders. The OG is a small structure and not detectable on medical imaging. The FO is easily identifiable on CT scans and the mandibular nerve on MRI, hence, the position of the OG may be predicted if the mean distance from the FO is known.

**Objective:** The objective is to describe the average distance between the FO and the OG in a sample of 18 infratemporal fossae from 21 cadavers.

**Methods:** A total of 21 high definition photographs of 21 infratemporal fossae from 18 cadavers were analyzed. The distance between the inferior edge of the medial part of the FO to the OG was measured.

**Results:** Four photographs of infratemporal fossae of four cadavers were excluded due to the inability to localize the inferior edge of the FO. A total of 15 infratemporal fossae from 17 cadavers were measured. The mean distance from the FO to the OG was 4.5 mm (SD 1.7), range 2.1–7.7 mm.

**Conclusions:** We have described the average distance from the OG to an easily identifiable anatomical landmark that is visible in CT scans, the FO. This anatomical study may aid in the development of strategies to localize the OG in order to explore its role as a therapeutic target for headache disorders.

## Keywords

foramen ovale, headache, otic ganglion, pterygopalatine ganglion, SPG, sphenopalatine ganglion

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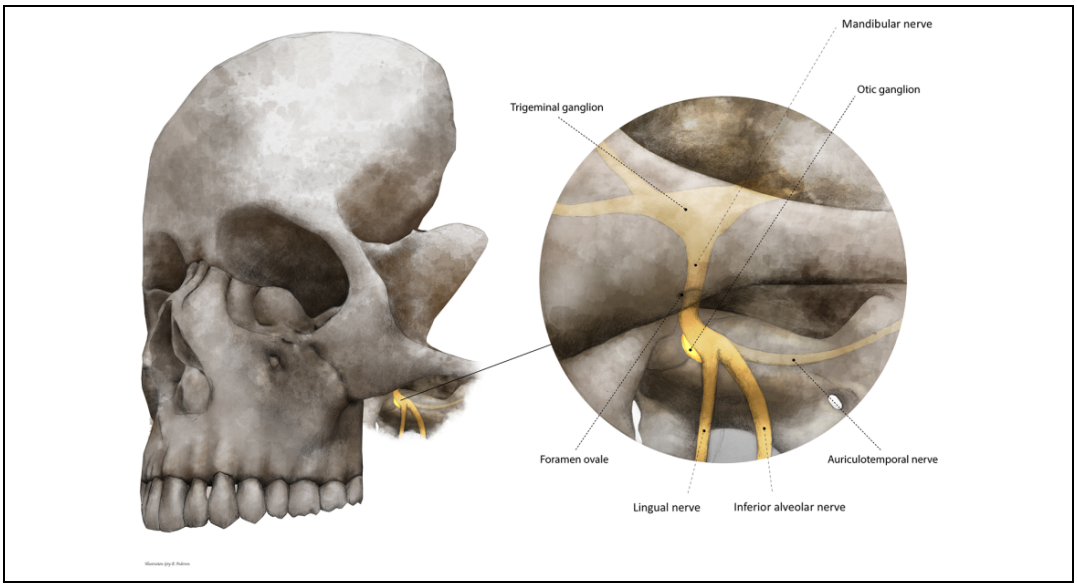


**Figure 1.** Location of the otic ganglion in the left infratemporal fossa. The OG is situated directly medial to the mandibular nerve under the foramen ovale. OG: otic ganglion.

## Introduction

Patients with trigeminal autonomic cephalalgias (TACs) and other headache disorders often experience cranial autonomic symptoms. Cluster headache is a prototypical example and patients often experience symptoms, such as miosis, conjunctival injection, ptosis, eyelid edema, epiphora, nasal congestion, and rhinorrhea.[1] Cranial autonomic symptoms in migraine are also common and have most likely been underestimated.[2] For instance, Riesco et al. found in a series of 100 patients with chronic migraine lacrimation in 49%, conjunctival injection in 44%, eyelid edema in 39% and nasal congestion in 20%.[3] Autonomic symptoms can be unilateral in 26.9% of patients with migraine.[2]

The sphenopalatine ganglion (SPG) is thought to be involved in the pathophysiology of TACs and other headache disorders, including migraine.[4] The SPG has been a target for the treatment of primary headache disorders for more than a century.[5] It receives its preganglionic parasympathetic fibers via the vidian nerve and the postganglionic fibers travel with the trigeminal nerve branches to innervate the mucous membrane of the nose, palate, tonsils, uvula, pharynx, lacrimal gland, and meningeal vessels.[4] Different approaches and several drugs have been used to block the SPG in a broad range of conditions.[4,6–8] A positive feedback loop from the trigeminocervical complex to the dural blood vessels involving the SPG has been described.[9]

In addition to the SPG, there are three other major parasympathetic ganglia in the cranium: the ciliary ganglion, the OG, and the submandibular ganglion.[10] The OG has received little attention from clinicians, and thus far, there have not been any therapeutic attempts at targeting this structure for the treatment of primary or secondary headache disorders.[10] Frey's syndrome may be the only known clinical entity related to the OG. The OG is a small structure (about 4 mm long, 3 mm wide, and 1.5 mm thick) located in the infratemporal fossa[11] (Figure 1). Its location and relationship to adjacent structures in humans have been described by Senger et al.[10] (Figure 2). In the inferior salivatory nucleus, preganglionic parasympathetic fibers exit the brain stem and travel through the glossopharyngeal nerve, the tympanic nerve, and the lesser petrosal nerve to reach the OG. The external sphenoidal nerve exits the OG with postganglionic fibers projecting toward the trigeminal ganglion and ganglia of the cavernous sinus.[10] This parasympathetic innervation of intracranial vessels from the OG has been shown in different animal models[12–14] and in humans.[15,16] In addition, the OG has been shown to be involved in the cranial vasomotor response.[17]

The role of the cranial parasympathetic system in primary headache disorders positions the OG as an interesting and potentially viable therapeutic target for the treatment of TACs and other headache disorders. To develop therapeutic strategies targeting the OG, it is important to understand its relationship with other structures that are easy to identify, such as the foramen ovale (FO), which can be easily localized on routine CT head scans. We have measured the distance from the FO to the OG in a series of photographs of anatomic preparations. This distance, not previously

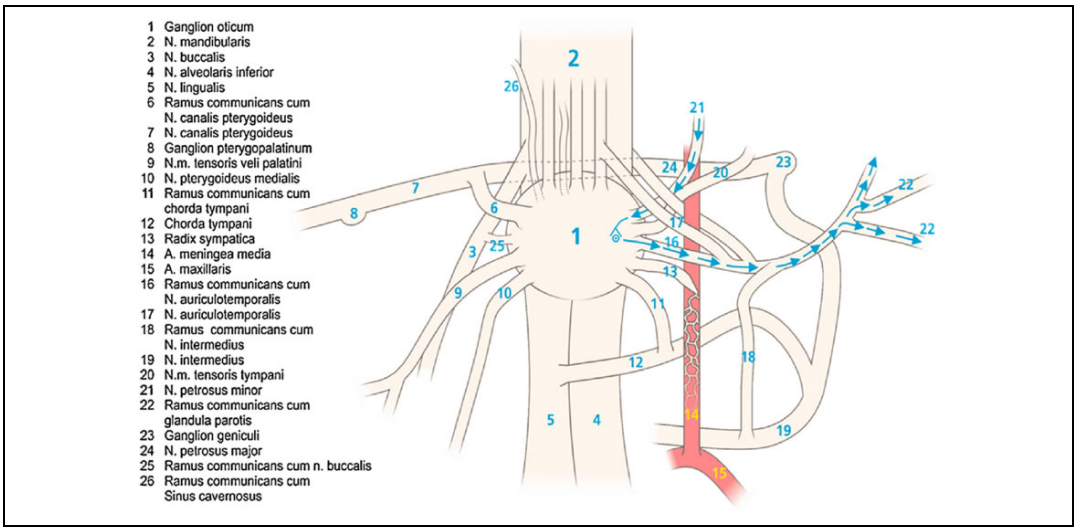


**Figure 2.** Illustration of the roots and branches of the otic ganglion, with permission from Senger et al.[10]

described in the literature, might be helpful for developing navigation-based therapies toward the OG.

## Methods

A total of 21 high-definition photographs of 21 infratemporal fossae from 18 cadavers were analyzed. The distance between the inferior edge of the medial part of the FO to the OG was measured.

An anatomical study using the same 21 halves of 18 human cadaveric heads was published by Senger et al.[10] In this study, the topography, syntopy, and morphology of the OG were described, though the distance from the FO to the OG was not documented.

The anatomical preparations had been used by students in the practical dissection course 2012/2013 at the Anatomical Institute of the University of Cologne (Germany).[10] All heads had been fixed in 10% aqueous formalin solution and sectioned in the midsagittal plane. The samples were not specified according to gender or age of the donor. The study by Senger et al. received authorization of the Ethics Committee of the Faculty of Medicine of the University of Cologne.[10] The cadaveric preparations were no longer available for analyses since they had been inhumed. For this reason, high-resolution photographs were used instead. These photographs were taken with a Nikon D50 and an Olympus DP21.

The approach used by Senger et al. to expose the OG in the preparations was by removing all structures that covered the OG from the medial side of the halved heads.[10] The structures removed from medial to lateral to reach the OG were the torus tubarius, the salpingopharyngeal muscle, the levator veli palatine, the tensor veli palatine, and the medial pterygoid muscle.[10]

To measure the distance from the FO to the OG on the photographs, we used free downloadable software for Mac OS, RulerSwift Version 1.0. All photographs had a reference scale situated in the same plane of measurement (Figure 3(a)). The distance was measured from the inferior aspect of the FO in its central part to the center of the OG. All measurements were performed by two researchers (JC and DB) and the mean results of the measurements are given.

### *Statistical analysis*

Stata/MP 15.1 for Mac (64-bit Intel, Copyright 1985-2017 StataCorp LLC) was used in the data analyses. Results are given as mean $\pm$ standard deviation if not otherwise stated.

### *Ethics approval and consent to participate/consent for publication*

This study used photographs of anatomical preparations obtained by Senger et al. Authorization for the use of these photographs was granted by the Ethics Committee of the Faculty of Medicine of the University of Cologne.

## Results

Four photographs of infratemporal fossae of four cadavers were excluded due to the inability to perform the measurements (in these four cases, it was not possible to localize the inferior part of the FO by JC and DB).

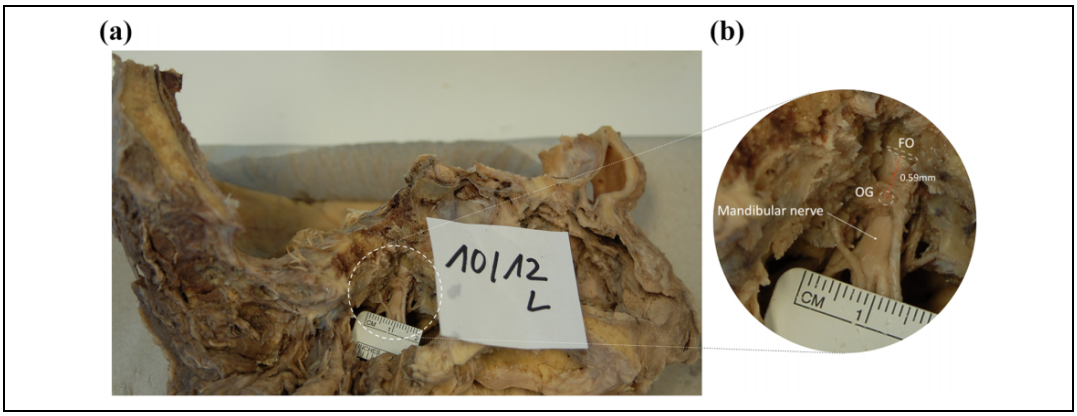


**Figure 3.** (a) Photograph showing an anatomic preparation of the left OG. (b) An enlargement of the same preparation with the measured distance between the inferior aspect of the FO and the OG (0.59 mm in this preparation). FO: foramen ovale; OG: otic ganglion.

**Table 1.** Results of the measurements between the inferior aspect of the foramen ovale and the otic ganglion.

| | Mean | Standard deviation | Range |
|---|---|---|---|
| Distance between FO and OG (mm) | 4.5 | 1.7 | 2.1–7.7 |

FO: foramen ovale; OG: otic ganglion.

A total of 15 infratemporal fossae from 17 cadavers were measured. The mean distance from the FO to the OG is presented in Table 1.

Figure 3(b) shows an example of the measured distance between the FO and the OG.

## Discussion

The OG's location and relationship to adjacent structures appear to be constant[10] (Figure 2). It is situated directly medial to the mandibular nerve (slightly ventral in some cases).[10] To develop therapeutic strategies targeting the OG, it is important to understand its relationship with other structures easy to identify in clinical practice. The mandibular nerve is easy to localize on MRI.[18] The relationship between the OG and an anatomical landmark, which would allow locating precisely the OG along the mandibular nerve and which is readily identifiable in clinical practice, has not been previously reported. In this study, we have seen that the OG is located directly caudally from the FO with an average distance of 4.5 mm. The FO is easy to localize in CT scans. The combination of these two anatomical landmarks (the mandibular nerve and the FO) might be of help when trying to predict the location of the OG.

A positive feedback "loop" from the trigeminocervical complex to the dural blood vessels has been described.[9] The efferent limb of the cranial parasympathetic system

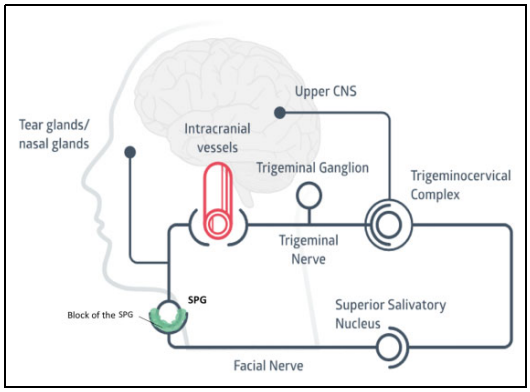


**Figure 4.** Illustration showing the assumed mechanism underlying how a block of the SPG works. SPG: sphenopalatine ganglion.

is activated either via a reflex arc from the trigeminal nucleus caudalis (from activated trigeminal nociceptors) or via descending modulatory influences from supraspinal and supratentorial structures, notably the hypothalamus.[19] This could lead to efferent activity, the release of vasoactive and inflammatory peptides at the level of the cranial vasculature and dura as well as the mucosal structures in the face.[19] This then, in turn, activates trigeminal afferents. A block of the SPG, therefore, affects efferent outflow and activation of the trigeminal sensory system peripherally (Figure 4).

The preganglionic parasympathetic fibers of the OG originate in the inferior salivatory nucleus and exit the brain stem via the glossopharyngeal nerve, then join the tympanic nerve, then the lesser petrosal nerve and synapse in the OG. The postganglionic fibers that are best documented are those exiting the ganglion toward the parotid

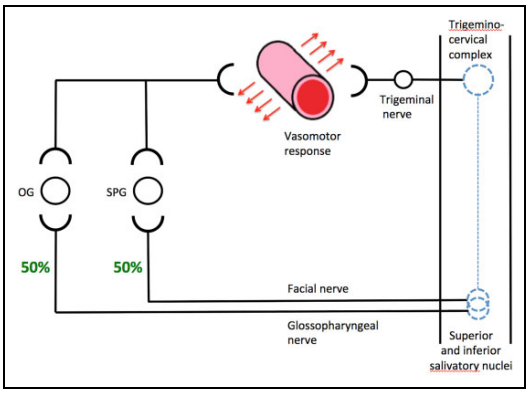


**Figure 5.** This illustration intents to summarize the findings by Goadsby et al., where it was observed that approximately 50% of the cranial vasomotor response in cats is mediated by the otic ganglion and the other 50% by the sphenopalatine ganglion.[17]

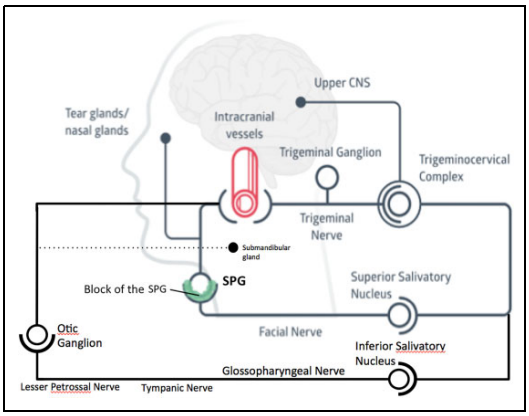


**Figure 6.** Illustration showing a proposed model of how the otic ganglion might be involved in the generation of trigeminoautonomic headaches.

gland through the auriculotemporal nerve. However, it is important to notice that other fibers leave the ganglion via the external sphenoidal nerve (in the literature also called dorsal rami, ganglionic cord, internal sphenoidal nerve, and rami communicantes cum sinus cavernosus).[10] 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 different animal models[12–14] and in humans.[15,16] Nociceptive fibers come in very close contact with parasympathetic and sympathetic fibers in the cavernous sinus.[20] This proximity of cranial parasympathetic fibers and trigeminal nociceptive fibers is relevant.[19] It has been documented that efferent fibers that innervate meningeal blood vessels and dura mater release neuropeptides, which directly and indirectly through inflammatory cascades activate nociceptive fibers and result in cephalic pain.[19] The cavernous sinus has been proposed to have a central role in cluster headache pathophysiology,[21] and cluster headache-like attacks have been reported in patients with lesions compressing or affecting the cavernous sinus.[22,23] In addition, it has been documented that roughly 50% of the cranial vasomotor response in cats is mediated by the OG and the other 50% by the SPG[17] (Figure 5).

Considering the work described above, we believe that there is evidence, both from an anatomical and a physiological point of view, that the OG might play a role in the pathophysiology of TACs and other headache disorders. We hypothesize that the loop described previously (between the trigeminocervical complex and dural vessels, see Figure 4) may be more complex than previously thought. The efferent part of this loop, in addition to the projections from the SPG, may also involve another efferent pathway: fibers from the inferior salivatory nucleus, which project to the OG via the glossopharyngeal nerve (Figure 6). John et al.[24] removed the SPG (histologically verified) in 13 patients with cluster headache,[24] but with no or only modest clinical effect: 7 patients had no effect, 4 had incomplete relief and only 2 had complete relief over the next 12 months. One may speculate that parasympathetic efferent signaling through the OG may be sufficient in some patients to maintain the above-mentioned positive feedback system to activate trigeminal nociceptive afferents through the same mechanism as SPG efferents. This may explain the incomplete response even when the SPG is blocked, radiated (gamma knife) or resected.

Despite the work described above, the SPG remains the only parasympathetic cranial ganglion targeted in headache. This might be due to anatomical differences, better-documented localization, and a general impression that the SPG is easier to target for interventions.[8]

## *Limitations of the study*

The main limitation of the study is that the measurements were not done in vivo but in cadavers and the measured distance may have changed due to postmortem desiccation or during the anatomic preparation.

The measurements of the distances between the FO and the OG were performed on photographs and not on the cadavers since they had been inhumed. These photographs might have a different angle on the trajectory of the mandibular nerve and this might affect the measurements of the distance between the FO and the OG. Four samples were excluded since we could not be sure that we had identified properly the inferior aspect of the FO in order to try to decrease the risk of error in our measurements.

Another limitation is that all cadavers were Caucasians and the measurements in other ethnicities may be different.

## Conclusions

We have described the average distance from the OG to an easily identifiable anatomical landmark on CT-scans, the FO. Cluster headache is one of the most severe pains described in the medical literature with a big burden for patients suffering from it.[25] Migraine is the first cause of disability in people under 50 years of age.[26] Patients suffering from TACs and other headache disorders are in need of new and better treatments. The identification of new targets is pivotal for the development of new treatments for these patients. The OG may become a future target in headache disorders. This anatomical study might be of help when trying to develop strategies targeting the OG. The topography of the OG in living human beings has not been described. Further anatomoradiological studies might be necessary in order to increase the efficacy, reliability, and safety of therapies targeting the OG.

Future research is needed to establish the role of OG in headache disorders. Studies in animal models to determine the possible function of the OG in the pathophysiology of headache are warranted. The feasibility and safety of a block of the OG have to be assessed in future studies.

## Clinical implications

- The OG might become a new target in headache disorders.
- The OG appears to have a constant location, being situated 4.5 mm inferior of the FO and medial to the mandibular nerve.
- The FO is easily localized on CT scans and may be an interesting anatomical landmark when trying to develop navigation-based therapies towards the OG.

### Authors' contributions

JC, DB, and ET had the original idea for the manuscript. JC and DB analyzed the data. JC reviewed the literature for the introduction and drafted the manuscript. DB, DD, MM, and ET assisted for drafting the manuscript and revision of the text. MS and DA revised the manuscript. All authors read and approved the final manuscript.

### Declaration of conflicting interests

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# Paper IV

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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

Joan Crespi, MD; Daniel Bratbak, MD, PhD; David W. Dodick, MD; Manjit Matharu, MD; Ole Solheim, MD; Sasha Gulati, MD; Erik Magnus Berntsen, MD; Erling Tronvik, MD

**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).

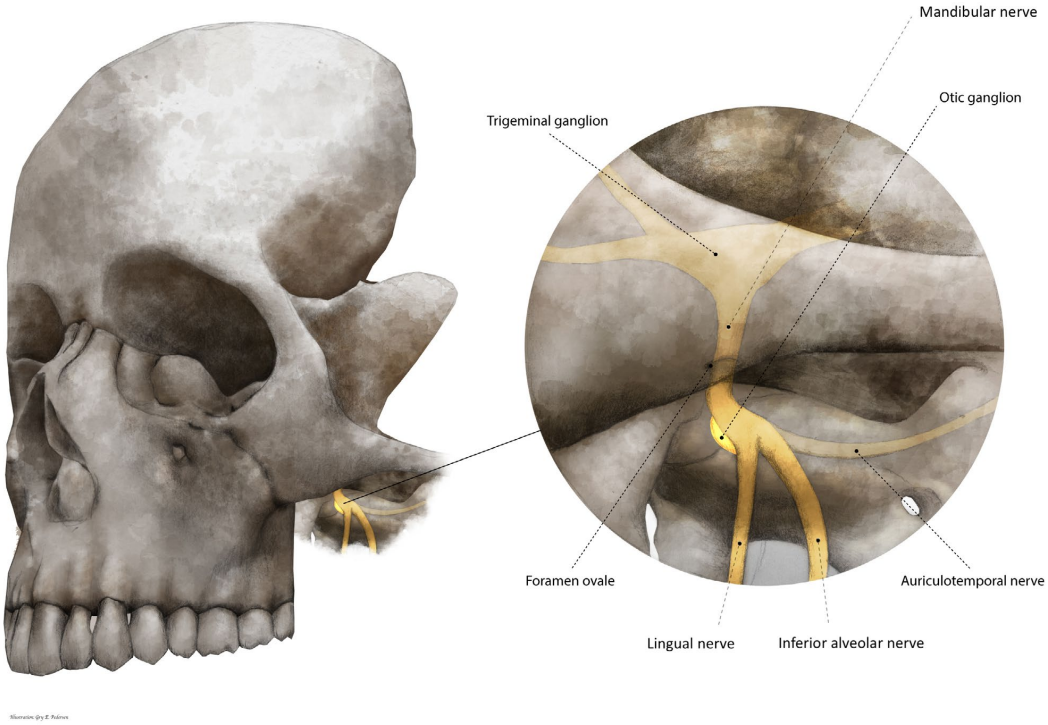


**Fig. 1.—Location of the otic ganglion (OG) in the infratemporal fossa.**

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.

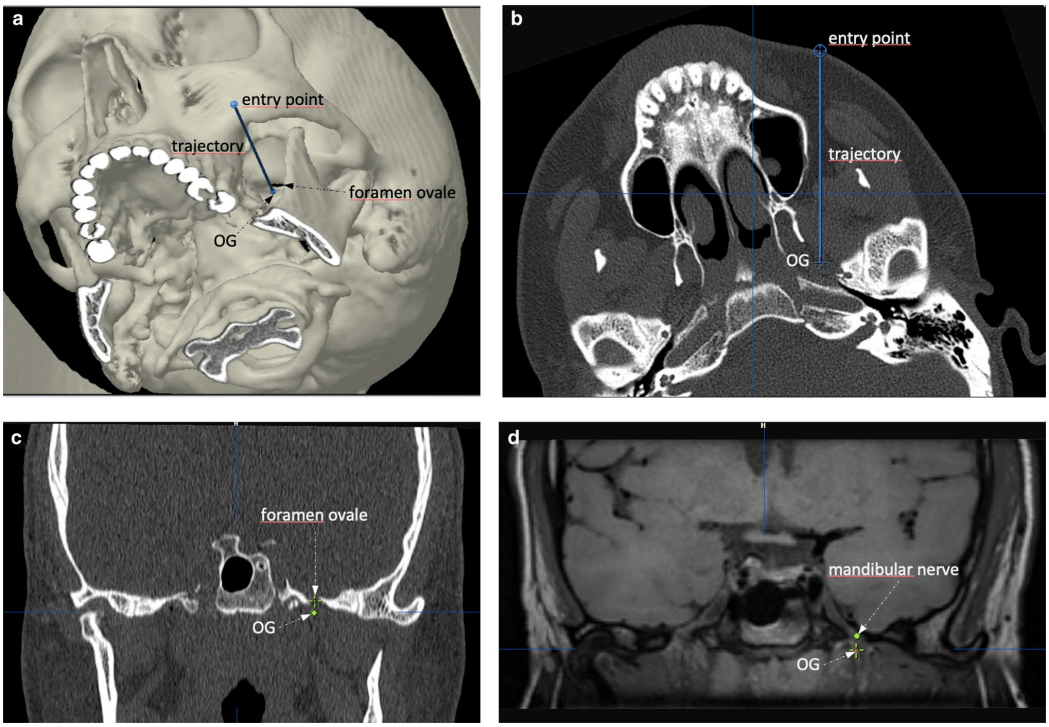


**Fig. 3.—Example of the trajectory planning in patient number 6. (a) 3D reconstruction of the trajectory toward the left OG (antero-infero-lateral view). (b) modified axial plan (trajectory-plan) on a CT scan to show the trajectory from the entry point to the left OG situated in the infratemporal fossa. (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)<br>Chin numbness<br>Dry mouth | 7.75 | −6.5% |
| 3† | 12.5 | Pain (injection side)<br>Jaw discomfort<br>Hyperacusis<br>Tinnitus<br>Ear fullness<br>Dry mouth | NA | NA |
| 4 | 12.5 | Dry mouth | 15.00 | −51.7% |
| 5† | 12.5 | Pain (injection side)<br>Chin numbness | NA | NA |
| 6 | 25 | Ear fullness<br>Discomfort swallowing<br>Articulation difficulties<br>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.

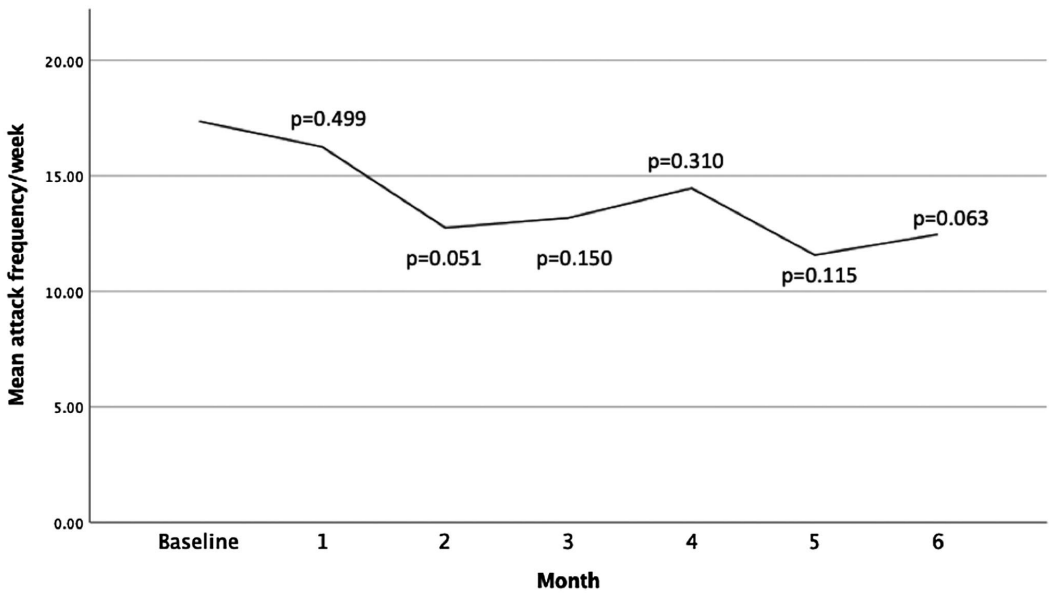


**Fig. 4.—Mean attack frequency per week over time.**

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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