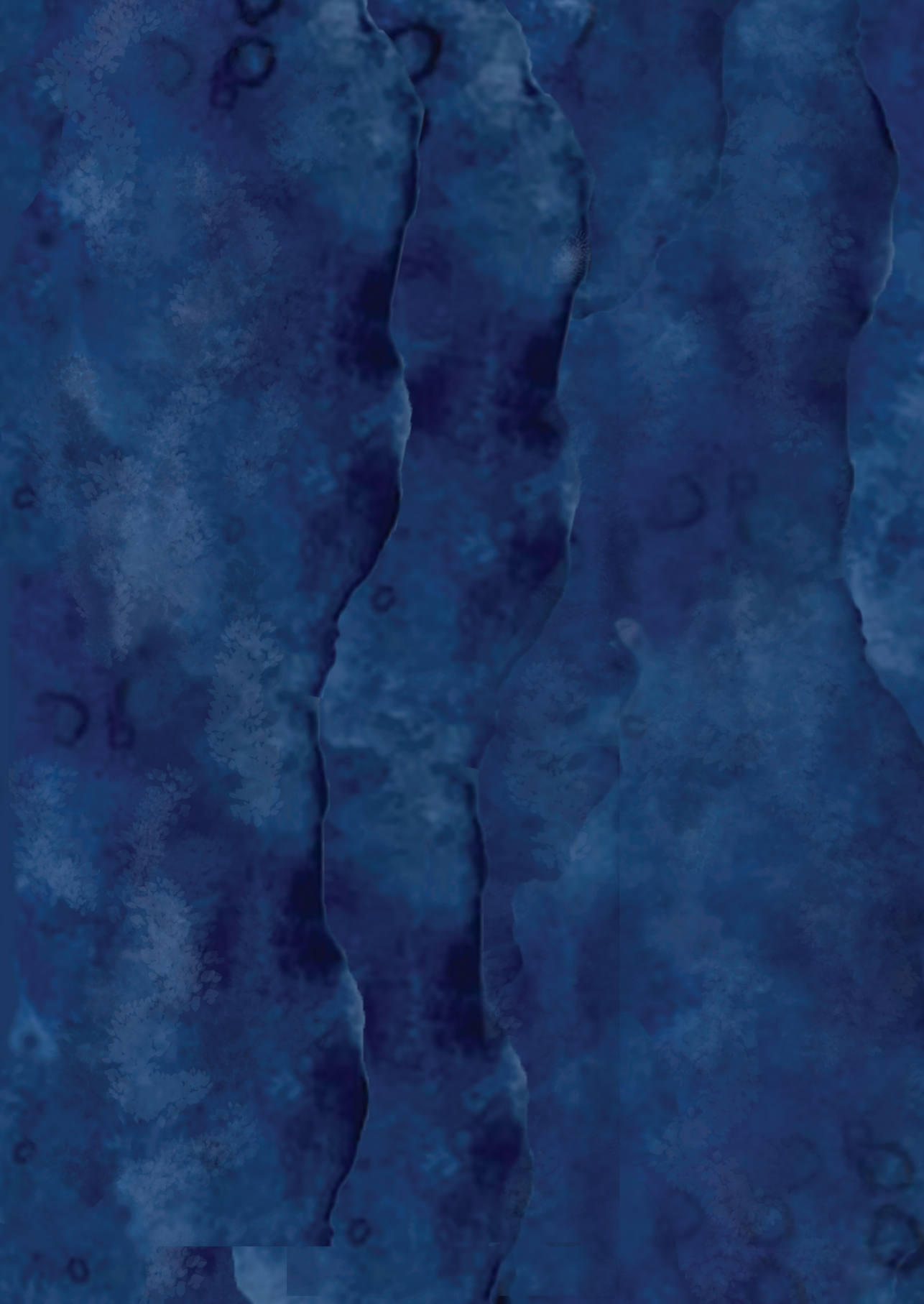
# Navigating the waves of cluster headache: clinical aspects and GON modulation

Naber, W.C.



# 9

# INFLUENCE OF GREATER OCCIPITAL NERVE INFILTRATION ON THE NOCICEPTIVE BLINK REFLEX IN CLUSTER HEADACHE

**Willemijn Naber, Paulien van Tilborg, Martijn Tannemaat, Marieke Niesters, Marieke Hellinga, Roemer Brandt, Rolf Fronczek**

Headache. 2025 Nov-Dec;65(10):1788-1799.

## ABSTRACT

### Objective

We aimed to explore the effect of greater occipital nerve (GON) infiltration on trigeminal transmission and its relation to clinical response. Infiltration of the greater occipital nerve with a local anesthetic and corticosteroids is effective in the treatment of both episodic (ECH) and chronic cluster headache (CCH). This effect is hypothesized to be due to delayed trigeminal transmission, resulting in a prolonged blink reflex with increased R2 latencies.

### Methods

In this single-center, prospective cohort study, participants with either ECH or CCH were followed 12 weeks post-GON infiltration with daily e-diary monitoring and nociceptive blink reflex measurements at four time points: 30 min before infiltration; and 30 min, 1, and 4 weeks post-infiltration. The primary outcome was the R2 latency. Secondary outcomes were attack frequency and intensity. Data were collected between October 2020 and March 2023.

### Results

A total of 33 participants were included in the primary analysis. No increased R2 latencies after GON infiltration were observed. When compared to baseline, daily attack frequency was significantly reduced during Week 1 (ECH: Δ -2.17 95% confidence interval [CI], -3.43 to -0.64; CCH: Δ -1.36, 95% CI -1.93 to -0.71) and Week 4 (ECH: Δ -2.90, 95% CI -3.86 to -1.36; CCH: Δ -1.57, 95% CI, -2.43 to -0.57), as was the attack intensity in Week 1 (ECH Δ-2.1, 95% CI, -3.4 to -0.9; CCH: Δ-1.5, 95% CI, -2.3 to -0.7) and Week 4 (ECH Δ-3.6, 95% CI, -6.4 to -0.8; CCH: Δ-1.7, 95% CI, -2.6 to -0.7) after GON infiltration compared to baseline. In all, 76% (25/33) of participants experienced a ≥30% reduction of their cluster headache attacks and 27% (9/33) were attack-free in Week 4. Unexpectedly, the R2 latency slightly decreased, but only in a solitary measurement ipsilateral to the infiltration side 4 weeks post-infiltration. No correlation between R2 latencies and clinical response were observed.

### Conclusion

The observed neurophysiological alterations were minor and were not associated with any clinical outcome. Therefore, despite rigorous analysis of multiple neurophysiological parameters in a relatively large patient sample, we did not find any evidence that the clinical response of GON infiltration is caused by reduced — or modulated — transmission of the trigeminal nerve or the trigeminal cervical complex. Although effective, the mechanism of the GON-infiltration thus remains enigmatic.

## INTRODUCTION

Cluster headache (CH) is a severe primary headache disorder characterized by 1 to 8 excruciating unilateral headache attacks per day that are accompanied by ipsilateral symptoms of autonomic dysfunction, (e.g., a red eye, tearing, nasal congestion, sweating in the face and ptosis) and/or restlessness.[1, 2] In episodic CH (ECH, 80% of cases), people have CH attacks several weeks to months at a time followed by a remission period without attacks. People with chronic CH (CCH, 20% of cases) have headache attacks with <3 consecutive months of remission per year.[2]

The pathophysiology of CH is partly understood, and the trigeminal-autonomic system and the hypothalamus are considered to be key players.[3, 4] Hypothalamic involvement is suggested by the evident circadian and seasonal rhythmicity, as well as by neuroimaging and neuroendocrinological findings. The hypothalamus regulates pain and autonomic symptoms through a two-way connection with the trigeminal cervical complex in the brainstem.[5, 6]

Treatment of cluster headache entails acute, prophylactic and transitional (temporary) treatment. One of the transitional treatments is infiltration around the greater occipital nerve (GON) with a corticosteroid and sometimes a local anesthetic.[7] Efficacy and safety have been demonstrated by several studies that recently led to the recommendation to use GON infiltration in the European Academy of Neurology cluster headache treatment guidelines. [8-11]

Despite its efficacy, the mechanism of action of GON infiltration in CH remains enigmatic. People with CH often experience tenderness in the neck in the region of the occipital nerve before the pain transgresses toward the peri-orbital region (V1 branch of the trigeminal nerve).[12, 13] This phenomenon could be explained by “referred pain” originating from the conjunction of afferent nerve endings of the trigeminal nerve and GON in the trigeminal cervical complex.[14-16] Therefore, it is hypothesized that GON infiltration affects trigeminal transmission within the trigeminal cervical complex, resulting in changes in CH symptoms.

This conjunction between the trigeminal cervical complex and the GON can be investigated with the blink reflex, which is facilitated by the trigeminal and facial nerves.[17] The blink reflex contains two main components: R1 and R2. An ipsilateral pontine component (R1), and a bilateral medullary component (R2) arise after stimulation of Aβ and Aδ afferent fibers, correlating with the closure of the eyelids.[17, 18] Earlier electrophysiological studies on trigeminal processing in CH produced conflicting results. However, most studies found impaired nociceptive processing at the level of

the brainstem.[19, 20]

In this study, we aimed to explore the effect of GON-infiltration on trigeminal transmission and its relation to clinical response. The impact of GON infiltration on the R2 component of the blink reflex was examined in relation to the clinical effects to infer whether the efficacy of the GON infiltration operates through the nociceptive fibers of the trigeminal nerve in the trigeminal cervical complex, as suggested by previous studies.[21] We hypothesize that GON infiltration delays trigeminal transmission, resulting in a prolonged blink reflex with longer R2 latencies and decreasing blink reflex strength, as determined by the area under the curves (AUCs) of the response.

## METHODS

### Design

This is a single-center, prospective cohort study where the effect of GON infiltration on trigeminal nociception and transmission was evaluated using the nociceptive blink reflex. Participants were followed for 12 weeks after the administration of a single injection with methylprednisolone (80 mg) and lidocaine (40 mg) around the GON. A daily headache e-diary was completed for 12 weeks and the blink-reflex was measured at four timepoints: (i) 30 minutes before GON infiltration and (ii) 30 minutes, (iii) 1 week and (iv) 4 weeks after the GON infiltration (Supplemental 1). Changes in prophylactic medication were according to standard treatment protocol and allowed during the entire study period and registered in the e-diary.

### Participants

All CH patients who were scheduled to receive an GON infiltration at the Leiden University Medical Center (LUMC) were screened for eligibility until the target of 41 participants was met. Participants were between 18 and 75 years with ECH or CCH and scheduled to receive a GON infiltration as standard care. Patients with a sphenopalatine ganglion or occipital nerve stimulator, or a known comorbidity affecting facial nerve conduction (e.g. peripheral nerve palsy) were excluded.
Written informed consent was obtained from all participants according to the Declaration of Helsinki and the study protocol was approved by the ethics committee of the LUMC (*Medisch Ethische Toetsings Commissie Leiden Den Haag Delft; NL71803.048.19*). Data were collected between October 2020 and March 2023.

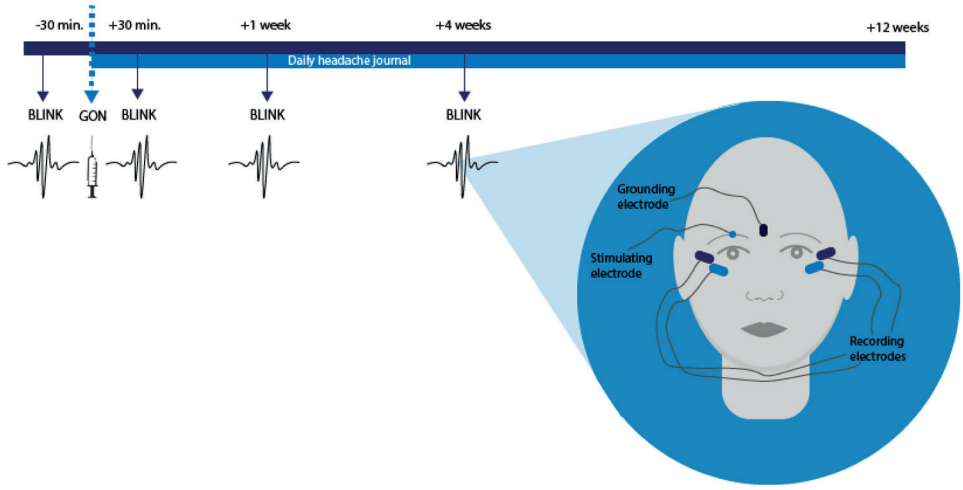
### Data collection

#### *Electrophysiology*

All measurements were performed in a standardized manner that employed a concentric planar electrode with central cathode and external anode ring (K2 concentric

ring stimulating electrode, 1.5 mm; Inomed, Emmendingen, Germany 22) positioned on the supraorbital foramen to stimulate the nociceptive blink reflex via the supraorbital nerve, utilizing the Nicolet Synergy EDX electromyography (EMG) machine (Supplemental 1). As opposed to a regular electrode, the concentric electrode specifically stimulates the superficial nociceptive nerve fibers.[18] A grounding electrode was placed at the root of the nose between the eyebrows. Surface electrodes were placed laterally and below the orbital bone on both sides. Stimulus pulse duration was 0.5 ms with a high-pass filter of 3 Hz and a low-pass filter of 10,000 Hz.

The sensitivity and pain thresholds were determined bilaterally by stepwise increments of the stimulation intensity with 0.39 mA until the electric stimulus was registered by the participant (sensitivity threshold) and increased until a pin prick like pain was felt (pain threshold). After determining the thresholds, no stimulus was given for 6.5 minutes to prevent habituation. Nociceptive blink reflexes were assessed bilaterally in sets of six measurements with a stimulus intensity of 1.5 times the pain threshold, each stimulus separated by intervals ranging from 15 to 20 seconds to prevent anticipation. The raw EMG signal was demeaned and rectified.




**Supplemental 1. Study protocol.**

In this single-center, prospective cohort study participants were followed for 12 weeks after infiltration of the GON with a daily headache e-diary and blink-reflex measurements at four timepoints: (i) 30 minutes before and (ii) 30 minutes after the GON infiltration, (iii) one week and (iv) four weeks after the GON infiltration. All measurements were performed in a standardized manner with a concentric planar electrode positioned on the supraorbital foramen, a grounding electrode at the root of the nose between the eyebrows and surface electrodes laterally and just below the orbital bone on both sides.

### *R2 latency and area under the curve (AUC) determination*

R2 latencies were manually determined by two independent evaluators (W.N., P.T.) in a standardized manner:

1. The overall quality of the measured blink reflex per visit was appraised to be "good", "moderate" or "poor". Visits with a "poor" quality blink-reflex were excluded. Participants were excluded from analysis if three or more visits were of "poor" quality.
2. The R2 latency was noted as the first deviation from baseline. If no R2 latency could be determined, it was recorded as missing.
3. R2 latencies were discussed by the evaluators until consensus was reached if: (i) the quality was "moderate", (ii) the R2 latencies differed > 10 ms between the evaluators or (iii) an evaluator harbored doubts about an assessment.

R2 latencies were labeled corresponding to the side they were stimulated (infiltration or non-infiltration side) and measured (ipsilateral or contralateral to the stimulation side), and split in four groups: infiltration side, ipsilateral (II); infiltration side, contralateral (IC); non-infiltration side, ipsilateral (NII) and non-infiltration side, contralateral (NIC).

The AUC was determined within a standardized window of 40 ms (R2 latency time – 5 ms; R2 latency time + 35 ms). The AUC is positively associated with the strength of the blink reflex (a reduced blink reflex results in decreased AUC). Calculating the AUC in units (μV x ms) from the raw EMG signal was done with custom-written software using Matlab 9.12 (*Mathworks, Natick, MA, USA*).

### *Clinical features*

Baseline characteristics were collected at the first visit. Participants completed a daily e-diary during the 12-week follow up that included all study parameters: attack frequency, intensity and duration, medication-use and general well-being on a 7-point Likert scale.

## Outcomes

The primary outcome was the mean change of the R2 latency of the blink reflex measured ipsilateral to the injection side between baseline and 1 week after the GON infiltration.

The key secondary outcome was the clinical response to GON infiltration, defined by the change in the average daily attack frequency and intensity.

Pre-specified tertiary outcomes were (i) the change of the area under the curve (AUC), (ii) the change of the trigeminal sensitivity and pain thresholds between all 4 time-points and (iii) the association between clinical response and the change in the blink reflex parameters: R2 latency, AUC and trigeminal sensitivity and pain thresholds.
Study parameters from the daily e-diaries were averaged per week to measure clinical response for each week during the 12-week follow up period. The clinical response in relation to blink measurements was calculated using data from e-diary entries of the 7 days prior to the visit date. Other clinical outcomes were: the median number of days to remission, defined as 7 consecutive days without attack; percentage of participants with prophylactic medication use for each week; percentage of participants that had a ≥30%, ≥50% or 100% attack frequency reduction at Week 4.

## Sample size calculation

A previous blink reflex study in CH showed a mean (standard deviation [SD]) R2 latency of 34.5 (3.9) ms before GON-infiltration.[21] To detect a mean of 39 ms after GON-infiltration with a power of 90% and a 5% bilateral significance threshold, a sample size of 10 participants was needed (using PS version 3.1.6 [https://github.com/vubiostat/ps] paired design, bilateral $\alpha$=0.05, $\sigma$ =3.9 ms, power = 0.9 [$\beta$=0.1] and $\Delta$=39−34.5=4.5 mg). Since GON-infiltration is only effective in two out of three infiltrations, 15 participants were needed to anticipate 10 responders. We planned to include 41 participants to allow for dropouts, possible variations in clinical effect and to be able to compare between ECH and CCH groups.

## Statistical Analysis

Distributions of continuous data were assessed visually in consultation with a statistician using histograms. Data are presented as mean and SD or as median and interquartile range (IQR) when appropriate for continuous variables and as number and percentage for categorical variables. The primary outcome was analyzed with a paired t-test, secondary and tertiary endpoints with a linear mixed model, a paired t-test or paired Wilcoxon rank test when appropriate. Baseline categorical data was analyzed with Pearson's chi-squared tests with Yates' continuity correction and baseline continuous data was compared using an independent samples t-test.

To determine the effect of the GON-infiltration, two linear mixed models were created and compared. The first linear mixed model was fitted to determine the influence of patient characteristics at baseline on the R2 latency. Secondly, the time-effect was added to the model as a proxy of the effect of the GON infiltration. Finally, the two models were compared with an ANOVA to determine the effect of the GON infiltration on the R2 latency. A significant difference between the two models suggests

that the time-effect, and thus GON infiltration, has a statistically significant influence on blink reflex parameters. The same methodology was used to determine the effect of the GON infiltration for the AUC.

Furthermore, a separate linear mixed model was fitted for the R2 latency and AUC for each measurement group (II, IC, NII, NIC) separately with participant as random effect and visit, age, sex and diagnosis as fixed effects. In consultation with a statistician, the assumptions of the linear mixed model, including the linearity of fixed effects, normality of residuals, residual homoscedasticity, and the normality of random effects, were assessed using the diagnostics plots (e.g. Q-Q plot and "residuals vs fitted") generated from the model.

A two-tailed $p<0.05$ was considered statistically significant. Because of the exploratory nature of our research no correction for multiple testing was applied. All analyses were performed using R version 4.3.1 (*R Foundation for Statistical Computing, Vienna, Austria*), version 4.3.1 in the RStudio Build 524 environment (*Posit PBC, Boston, MA, USA*), and the "*lme4*" version 1.1.35.1 package was used to fit linear mixed-effects models.

## RESULTS

### Participants

Out of 146 screened, 41 participants were enrolled in the study (Figure 1). Of these, 33 participants were included for the primary analysis, 33 in the e-diary analysis and 28 were included in the secondary and tertiary analysis. Reasons for exclusions are listed in Figure 1.

Clinical baseline characteristics are depicted in Table 1. In all, 17 (52%) participants with ECH and 16 (49%) with CCH were included in the primary analysis. Most blink measurements were conducted at the exact timepoint relative to the GON infiltration, with a few outliers for the Week 1 and Week 4 visit respectively (range: 6-11 days and 25-40 days after GON infiltration). The e-diary compliance was good: on average participants completed 90% of the daily e-diaries during follow up.

### R2 latency

No increase in the mean II R2 latency was observed 30 minutes or 1 week after GON infiltration compared to baseline (Figure 2). Unexpectedly, the R2 latency slightly decreased with 2.02 ms at 4 weeks post-infiltration, but only in a solitary measurement ipsilateral to the infiltration (95% confidence interval [CI] 0.20 to 3.84 ms, $p=0.031$). The GON-infiltration did not affect the R2 latency in the overall linear mixed model

**Table 1. Baseline characteristics for participants with episodic and chronic cluster headache.**

| | Total (N=33) | ECH (N=17) | CCH (N=16) | P-value |
|---|---|---|---|---|
| Age, years, mean ± SD | 45.6 ± 14.5 | 48.2 ± 13.8 | 42.9 ± 15.2 | 0.295 |
| Female, n (%) | 9 (27) | 3 (18) | 6 (38) | 0.374 |
| Attack frequency*, IQR | 2 [1- 4] | 2 [1-5] | 2 [2 – 3] | 0.912 |
| Attack intensity, NRS (IQR) | 7 [5.0-8.0] | 7 [5.0- 8.0] | 7 [6.8- 8.3] | 0.318 |
| Using Prophylactic medication, n(%) | 13 (40) | 6 (35) | 7 (44) | 0.770 |
| *Verapamil, n* | *10* | *6* | *4* | |
| *Topiramate, n* | *2* | *0* | *2* | |
| *Frovatriptan, n* | *1* | *0* | *1* | |
| **Right sided pain, n (%)** | **21 (64)** | **12 (71)** | **9 ( 56)** | **0.622** |

Legend: ECH: Episodic Cluster Headache; CCH: Chronic Cluster Headache; IQR: Interquartile range; NRS: Numeric rating scale; SD: Standard deviation. *Attack frequency = median daily attack frequency

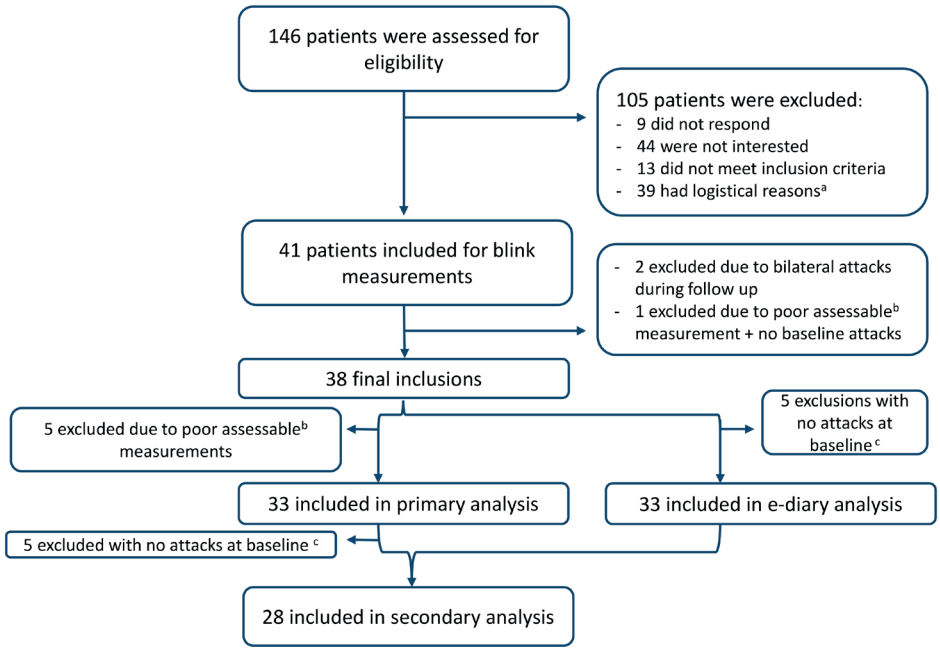



**Figure 1. Study flow chart of the inclusion process.**

Out of 41 participants who were enrolled for blink measurements, 33 were included for the primary analysis about the effect of GON infiltration on the R2 component of the blink reflex. In all, 28 were included for the secondary analysis about the effect of GON infiltration on the AUC component of the blink reflex and the possible association between clinical outcome and changes in the blink reflex. [a] Logistical reasons mainly included travel distance to the study site and scheduling problems with the GON infiltration. [b] Poor assessable measurements: poor quality of the blink reflex as appraised by two independent evaluators. [c] Five participants had no attacks at baseline and were therefore excluded from e-diary and secondary analysis.

**Table 2. Results of linear mixed models with change in R2 latency over time compared to baseline for each measurement.**

| | β | 95% CI | *p*-value |
|---|---|---|---|
| *Infiltration side, ipsilateral (II)* | | | |
| 30 minutes | -1.07 | -3.03 to 0.88 | 0.288 |
| Week 1 | -0.79 | -2.76 to 1.18 | 0.438 |
| Week 4 | -2.13 | -4.14 to -0.15 | **0.041*** |
| Age | -0.07 | -0.16 to 0.03 | 0.182 |
| Female | -2.41 | -5.38 to 0.56 | 0.136 |
| Subtype (CCH) | 1.01 | -1.69 to 3.70 | 0.486 |
| *Infiltration side, contralateral (IC)* | | | |
| 30 minutes | -0.41 | -2.27 to 1.46 | 0.672 |
| Week 1 | -0.15 | -2.03 to 1.73 | 0.876 |
| Week 4 | -1.14 | -3.06 to 0.74 | 0.245 |
| Age | -0.11 | -0.20 to -0.02 | **0.035*** |
| Female | -1.32 | -4.23 to 1.59 | 0.396 |
| Subtype (CCH) | 0.93 | -1.71 to 3.57 | 0.511 |
| *Non- Infiltration side, ipsilateral (NII)* | | | |
| 30 minutes | -1.29 | -3.06 to 0.47 | 0.157 |
| Week 1 | -1.50 | -3.30 t0 0.30 | 0.108 |
| Week 4 | -0.97 | -2.77 to 0.83 | 0.297 |
| Age | -0.13 | -0.21 to -0.04 | **0.010*** |
| Female | -1.42 | -4.21 to 1.37 | 0.345 |
| Subtype (CCH) | 0.81 | -1.72 to 3.34 | 0.549 |
| *Non- Infiltration side, contralateral (NIC)* | | | |
| 30 minutes | -1.24 | -3.06 to 0.57 | 0.187 |
| Week 1 | -1.17 | -3.02 to 0.68 | 0.221 |
| Week 4 | -0.48 | -2.33 to 1.37 | 0.617 |
| Age | -0.11 | -0.19 to -0.04 | **0.008**** |
| Female | -0.98 | -3.35 to 1.39 | 0.442 |
| Subtype (CCH) | -0.49 | -2.64 to 1.65 | 0.667 |

CI: confidence interval, β: regression coefficient, CCH: Chronic cluster headache. *$p < 0.050$, **$p < 0.010$

(X2= 12.62; df= 12; $p$= 0.397, Supplemental 2). No increase in R2 latencies were found for any of the visits in the linear mixed models for each of the R2 latency groups (II, IC, NII, NIC). An unexpected small decrease in R2 latency was observed in Week 4, but only for the II measurements (β = -2.13 ms, 95% CI -4.14 to -0.15, $p$ =0.041; Table 2). There was no difference in the mean R2 latency between the infiltration side and the non-infiltration side at baseline (Supplemental 3).

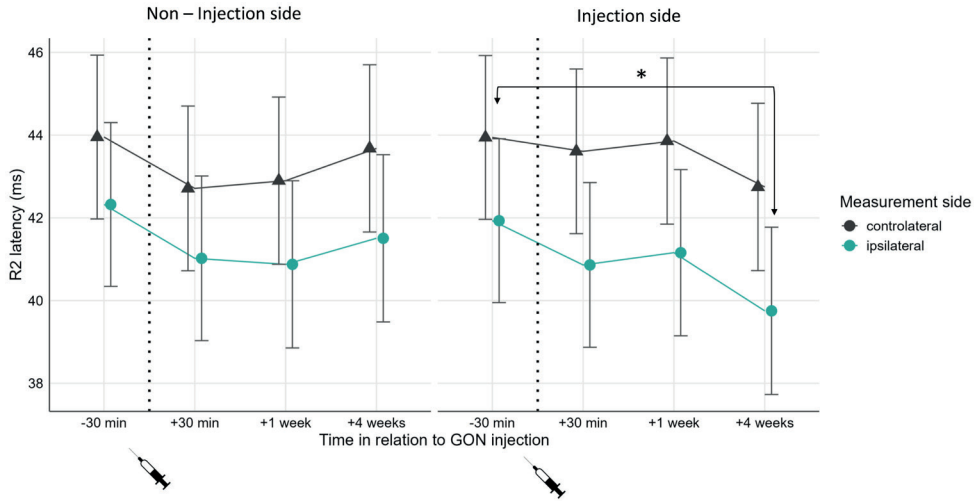



**Figure 2. Mean R2 latency times with 95% confidence interval before and after GON infiltration.**

The estimated marginal means of the R2 latencies with the 95% confidence intervals at four timepoints: 30 min before infiltration and 30 min, 1 week, and 4 weeks post-infiltration. The blink reflex was stimulated on the same side as the infiltration (= infiltration side) or the opposite side (= non-infiltration side). The R2 latency was measured bilaterally, ipsilateral and contralateral to the stimulation side. The dotted line depicts the GON infiltration.* The blink reflex R2 latency measured on the infiltration side, ipsilateral (II) was significantly lowered 4 weeks after the GON infiltration compared to 30 min before.

## Attack frequency

The median daily attack frequency decreased significantly from baseline in Week 1 and Week 4 after GON infiltration for ECH (Week 1: Δ -2.17, 95% CI -3.43 to -0.64; Week 4: Δ -2.90, 95% CI -3.86 to -1.36) and CCH: (Week 1: Δ -1.36, 95% CI -1.93 to -0.71; Week 4: Δ -1.57, 95% CI -2.43 to -0.57) and throughout the 12-week follow-up (Table 3, figure 3).

A ≥30% attack reduction in Week 4 was observed in 76% (25/33) of participants (ECH: 87% [13/15], CCH: 67% [12/18]), a ≥50% reduction in 67% (22/33) of participants (ECH: 87% [13/15], CCH: 50% [9/18]) and attack-freedom in 27% (9/33) of participants (ECH: 53% [8/15], CCH: 6% [1/18]. The median (IQR) number of days until remission was 29 (15- 84) days (Figure 4).

## Attack intensity

Attack intensity decreased in Week 1 and Week 4 after GON infiltration compared to baseline for ECH (Week 1: Δ-2.1, 95% CI -3.4 to -0.9; Week 4: Δ-3.6, 95% CI -6.4 to -0.8) and for CCH (Week 1: Δ-1.5, 95% CI -2.3 to -0.7; Week 4: Δ-1.7, 95% CI -2.6 to -0.7) and remained lower throughout the 12-week follow up (Figure 5a, Supplemental 4).

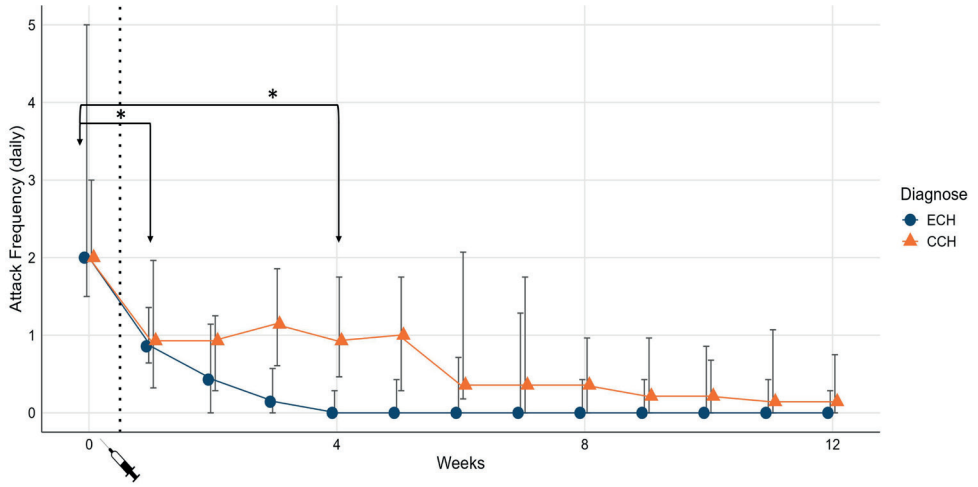



**Figure 3. Median daily attack frequency during 12-week follow up after GON infiltration.**

Median daily attack frequency and interquartile ranges (IQR) at baseline and in the 12 weeks following the GON infiltration. The dotted line depicts the GON infiltration. A statistically significant reduction in median daily attack frequency was observed in week 1 and 4 compared to baseline. ECH: episodic cluster headache. CCH: chronic cluster headache.

**Table 3. Change in attack frequency after GON infiltration.**

| | Attack frequency† (IQR) | Estimate (95%CI) | Wilcoxon test statistic (V) | *p*-value |
|---|---|---|---|---|
| **Cluster headache (N=33)** | | | | |
| Baseline | 2.0 (2.0 - 4.0) | | | |
| Week 1 | 1.0 (0.4 - 1.6) | 1.57 (0.90 - 2.36) | 495.0 | **<0.001*** |
| Week 4 | 0.4 (0.0 - 1.4) | 1.93 (1.29 - 2.86) | 474.0 | **<0.001*** |
| **Episodic Cluster headache (N=15)** | | | | |
| Baseline | 2.0 (1.5 - 5.0) | | | |
| Week 1 | 1.0 (0.6 - 1.4) | 2.17 (0.64 - 3.43) | 109.5 | **0.005*** |
| Week 4 | 0.0 (0.0 - 0.3) | 2.90 (1.36 - 3.86) | 120.0 | **<0.001*** |
| **Chronic Cluster headache (N=18)** | | | | |
| Baseline | 2.0 (2.0 - 3.0) | | | |
| Week 1 | 0.9 (0.3 - 2.0) | 1.36 (0.71 - 1.93) | 146.0 | **0.001*** |
| Week 4 | 1.3 (0.5 - 2.0) | 1.57 (0.57 - 2.43) | 120.0 | **0.005*** |

Results of paired Wilcoxon rank tests between changes in the daily attack frequency at one and four weeks after GON infiltration compared to baseline in participants with episodic or chronic cluster headache.
Legend: CI: Confidence interval, IQR: interquartile range *P ≤ 0.050 † Median of the daily attack frequency.

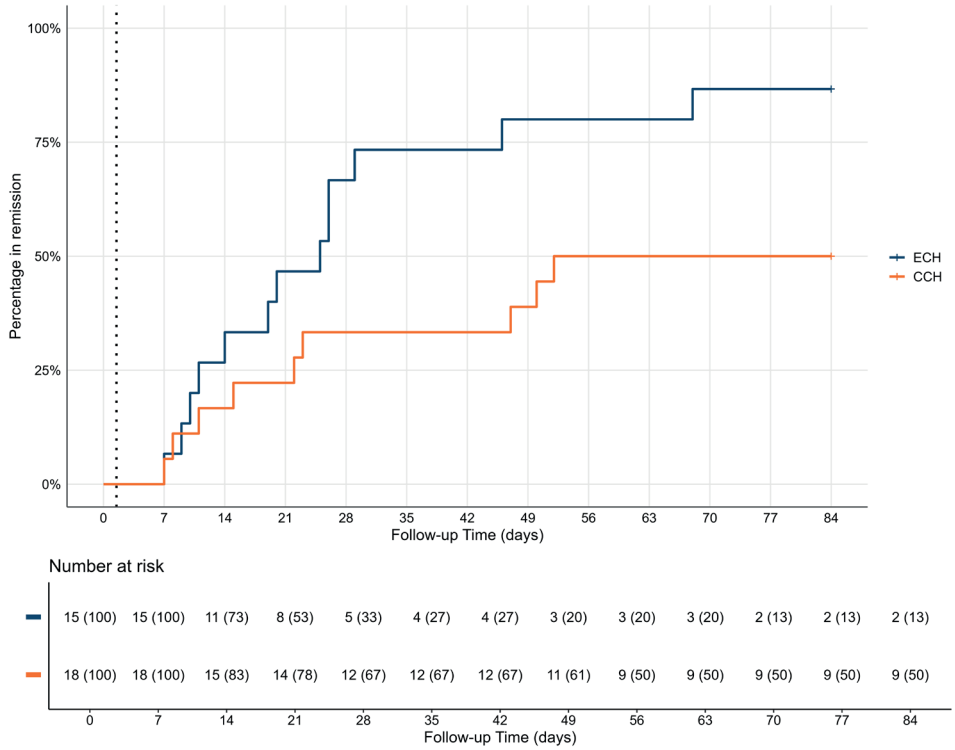



**Figure 4. Percentage of participants reaching remission during follow up.**

Kaplan Meijer curve depicting the percentage of participants that had remission of their cluster headache following a GON infiltration. Remission is defined as 7 consecutive attack-free days. ECH: episodic cluster headache; CCH: chronic cluster headache.

## The overall wellbeing

The most reported score for overall wellbeing improved from 4 out of 6 during the first week to 5 out of 6 during the fourth week. The increasing wellbeing was observed in both groups, but wa most pronounced in ECH participants during the 12-week follow up (Figure 5b)

## Tertiary outcomes

### *Change of the area under the curve (AUC) between all 4 time-points*

There was no decrease in the AUC at any of the four timepoints, but a slight increase was observed 1 week and 4 weeks after GON infiltration compared to baseline ( II AUC: Δ 11530.75 µVms, 95 CI% 22262.5 to 700.0, $p$ = 0.036; Δ 12167.25 µVms, 95% CI 18842.0 to 4194.0, $p$= 0.006; Figure 6, Supplemental 2 and 5).

### *Change in sensitivity and pain threshold*

There were no changes in the sensitivity and pain thresholds at any of the time-points, except for a decrease in the sensitivity threshold in Week 4 that was not

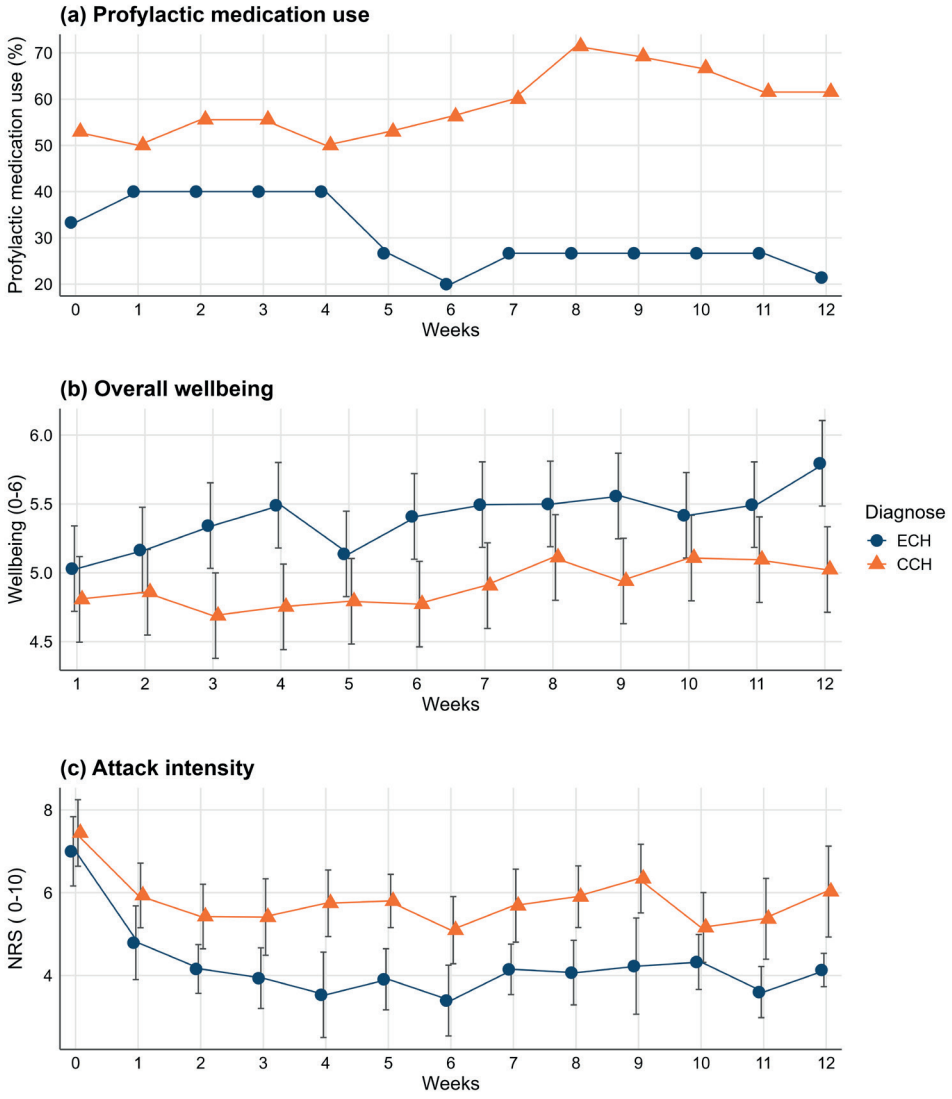



**Figure 5. Cluster headache features after GON infiltration.**

Clinical features of cluster headache during 12-week follow up after GON infiltration.
(A) Proportion of participants using prophylactic medication.
(B) Overall wellbeing on a scale of 0-6, presented as mean + standard deviation (SD).
(C) Attack intensity on a numeric rating scale(NRS) of 0-10, presented as mean + SD.

mirrored in the pain threshold (-0.12, 95% CI -0.23 to -0.01; Supplemental 6). There were no significant changes in right or left stimulus strength over time (respectively, *p*= 0.691 and *p*=0.303; Supplemental 7).

### *Correlation clinical response and blink reflex parameters*

There was no association between the change in median daily attack frequency in relation to the change of the R2 latency, AUC or the sensitivity and pain threshold.

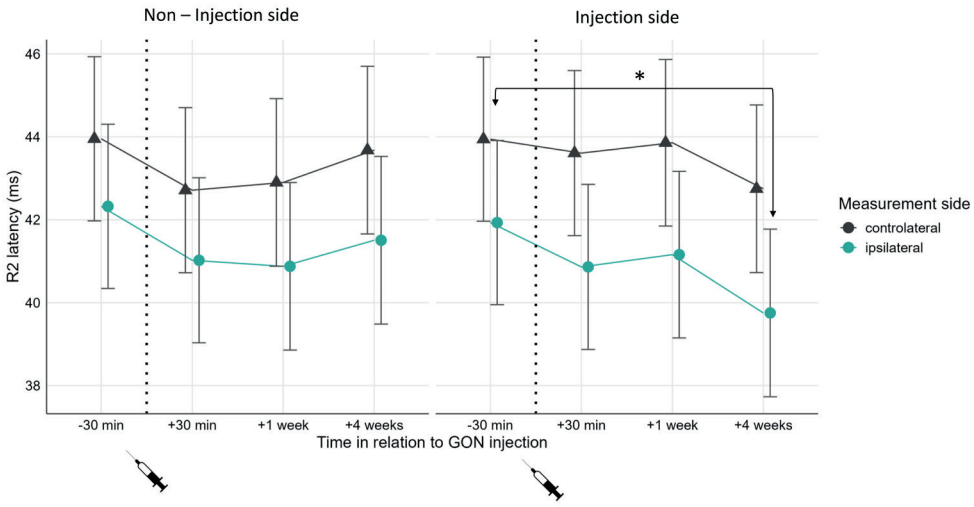



**Figure 6. Median Area Under the Curves (AUC) of the blink reflex before and after GON infiltration.**

Median Area Under the Curves (AUC) of the blink reflex with the 95% confidence intervals as measured at four timepoints: 30 min before infiltration and 30 min, one week, and four weeks post-infiltration. The blink reflex was stimulated on either the same side as the infiltration (=infiltration side) or the opposite side (=non-infiltration side) and the R2 latency was measured bilaterally, ipsilateral and contralateral to the stimulation side. The dotted line depicts the GON infiltration. * The median AUC increased one week and four weeks after the GON infiltration compared to baseline on the infiltration side, measured ipsi- and contralateral. The median AUC increased four weeks after the GON infiltration compared to baseline on the non-infiltration side, measured ipsi- and contralateral.



## DISCUSSION

Although we could not detect changes in the nociceptive blink reflex, this prospective open-label study shows that GON infiltration with methylprednisolone and lidocaine around the GON is an effective treatment for both ECH and CCH. Within 4 weeks, more than two-thirds of participants with CCH had a reduction in attack frequency of ≥30%, and over half of the participants with ECH were attack free. Furthermore, attack intensity decreased and overall wellbeing improved in both ECH and CCH during the 12-week follow up.

However, these beneficial effects were not associated with corresponding changes in the nociceptive blink reflex. No neurophysiological changes were found that supported our hypothesis that the blink reflex is reduced after GON infiltration.

At none of the timepoints did R2 latencies increase. Unexpectedly, after 4 weeks a small decrease in R2 latencies was observed, but this finding was limited to the ipsilateral measurement on the injection side. Several factors could explain this alteration, but a correlation with GON infiltration or reduction in CH symptoms appears unlikely as the increase was not confirmed in more comprehensive models, and no correlation was found between clinical symptoms and the blink reflex. Stimulus strengths were stable during measurements and could not explain the change. Sleep deprivation and negative emotions such as anxiety, are sometimes implied to increase the blink reflex, but this seems an unlikely explanation since the participants were generally feeling better 4 weeks post-infiltration compared to baseline. The finding could be a spurious, false positive result, since the change was only slightly outside the confidence interval and we did not correct for multiple testing due to the explorative character of this study.

No changes in the AUC were found that confirmed our hypothesis. Only a slight increase 1 and 4 weeks after GON infiltration was observed, but this change was not robustly reflected in the more reliable R2 outcome and the AUC is known to be more susceptible to external influence. In conclusion, as the observed neurophysiological alterations did not show an association with any clinical outcome, it seems unlikely that the clinical response of GON infiltration is caused by reduced —or modulated— transmission of the trigeminal nerve or the trigeminal cervical complex.

Our observations are in contrast with a previous study from Busch et al., which reported an increased R2 latency and decreased AUC directly after GON infiltration on the injection side without a corresponding significant clinical improvement.[14, 21] The contrasting results could be explained by the difference in injection compound (prilocaine 50 mg vs. lidocaine 40 mg + methylprednisolone 80 mg). Current understanding suggests that corticosteroids, rather than anesthetics, are the primary agents responsible for the efficacy of GON infiltration in CH.[8] Therefore, the evident clinical effect observed in our study, and the lack of clinical effect after infiltration with only prilocaine, can likely be attributed to the injected corticosteroid. As both studies did not show a correlation between clinical effect and neurophysiological changes, it appears that the mechanisms by which GON infiltration improves CH symptoms follows a more complex, yet to be discovered, pathway that does not primarily includes an altered trigeminal transmission.

The key strength of this study lies in its focused investigation into the mechanism of action of GON infiltration in CH. The prospective design using repeated blink measurements and daily e-diary monitoring during the 12-week follow up ensured that both clinical and neurophysiological changes were recorded in a standardized and detailed manner. This provides unique real-world data on the effectiveness of GON injections in patients undergoing treatment through regular care. In addition, it allows for the investigation of the correlation between neurophysiological and clinical changes, whereas previous studies primarily explored either clinical changes after GON infiltration or focused solely on neurophysiological changes.

## Limitations

Some limitations should be discussed. First, the primary outcome (R2 latency) was determined manually and therefore sensitive to observer bias. To limit this bias, R2 latencies were scored independently by two well-trained evaluators in a systematic manner. If any doubt arose, consensus was reached between the evaluators or the measurement was excluded. This system ensured that only clear, well-performed blink reflexes were included, maintaining high quality of our data.

Second, clinical results regarding the efficacy of GON infiltration as CH therapy could be overestimated due to the prospective open-label design, and participant selection. A placebo effect cannot be excluded and a selection bias could have occurred through the selection of participants who were prescribed a GON infiltration through regular care. This cohort probably consists of a higher proportion of GON responders compared to a random sample.

Third, clinical response in ECH could be overestimated in this study since no additional inclusion criteria regarding the timing of the episodes in relation to the GON infiltration were used. The cluster episodes could have ended due to their natural course. However, this effect is expected to be limited since (i) it is common practice in our hospital to administer the GON infiltration at the start of a cluster episode; (ii) the GON infiltration was effective within the first week, which is unlikely to coincide with the end of the episode; and (iii) a similar curve and response-time was seen in CCH.

Fourth, the use of additional prophylactic medication (e.g., verapamil) was allowed during the study follow-up. It is impossible to determine exactly how much of the observed effect can be attributed to GON infiltration or to prophylactic medication. However, as the total prophylactic medication use decreased during the period in which the highest clinical response was observed, it is likely the GON infiltration is largely responsible for this clinical improvement. Even taking in account these

limitations, the clinical response is still striking since they provide “real world data” in a relatively well-defined and homogenous cohort. This bridges the gap between clinical trial data and their translation into clinical practice.

### Conclusion

In conclusion, GON infiltration with 80 mg methylprednisolone and 20 mg lidocaine appears to be a very effective transitional add-on therapy for both ECH and CCH in a real-world setting. Despite rigorous analysis of multiple neurophysiological parameters in a relatively large patient sample, we did not find any evidence that the clinical response of GON infiltration is caused by reduced - or modulated - transmission of the trigeminal nerve or the trigeminal cervical complex. Although effective, the mechanism of the GON-infiltration thus remains enigmatic.

## ARTICLE HIGHLIGHTS

- GON infiltration with 80 mg methylprednisolone and 20 mg lidocaine appears to be a very effective transitional add-on therapy for both ECH and CCH.
- Despite rigorous analysis, we did not find any evidence that the clinical response of GON infiltration is caused by reduced - or modulated - transmission of the trigeminal nerve or the trigeminal cervical complex.
- Although effective, the mechanism of the GON-infiltration thus remains enigmatic.

## REFERENCES


1. Drummond PD. Mechanisms of autonomic disturbance in the face during and between attacks of cluster headache. Cephalalgia. 2006;26(6):633-41.
2. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-
3. Goadsby PJ. Pathophysiology of cluster headache:a trigeminal autonomic cephalgia. Lancet Neurol. 2002;1(4):251-7.
4. Wei DY, Yuan Ong JJ, Goadsby PJ. Cluster Headache: Epidemiology, Pathophysiology, Clinical Features, and Diagnosis. Ann Indian Acad Neurol. 2018;21(Suppl 1):S3-s8.
5. May A, Schwedt TJ, Magis D, Pozo-Rosich P, Evers S, Wang SJ. Cluster headache. Nat Rev Dis Primers. 2018;4:18006.
6. Leone M, Bussone G. Pathophysiology of trigeminal autonomic cephalalgias. Lancet Neurol. 2009;8(8):755-64.
7. Leroux E, Ducros A. Occipital injections for trigemino-autonomic cephalalgias: evidence and uncertainties. Curr Pain Headache Rep. 2013;17(4):325.
8. Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. Pain. 2005;118(1-2):92-6.
9. Leroux E, Valade D, Taifas I, Vicaut E, Chagnon M, Roos C, et al. Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial. Lancet Neurol.2011;10(10):891-7.
10. Brandt RB, Doesborg PGG, Meilof R, de Coo IF, Bartels E, Ferrari MD, et al. Repeated greater occipital nerve injections with corticosteroids in medically intractable chronic cluster headache: a retrospective study. Neurol Sci. 2022;43(2):1267-72.
11. May A, Evers S, Goadsby PJ, Leone M, Manzoni GC, Pascual J, et al. European Academy of Neurology guidelines on the treatment of cluster headache. Eur J Neurol. 2023;30(10):2955-79.
12. Torelli P, Cologno D, Cademartiri C, Manzoni GC. Application of the International Headache Society classification criteria in 652 cluster headache patients. Cephalalgia. 2001;21(2):145-50.
13. Schor LI, Pearson SM, de Castro Sousa B, Ettore U, Rohrer U, Gu Y, et al. The location of pain in cluster headache: Data from the International Cluster Headache Questionnaire. Headache. 2024;64(7):783-95.
14. Busch V, Jakob W, Juergens T, Schulte-Mattler W, Kaube H, May A. Functional connectivity between trigeminal and occipital nerves revealed by occipital nerve blockade and nociceptive blink reflexes. Cephalalgia. 2006;26(1):50-5.
15. Pfaller K, Arvidsson J. Central distribution of trigeminal and upper cervical primary afferents in the rat studied by anterograde transport of horseradish peroxidase conjugated to wheat germ agglutinin. J Comp Neurol. 1988;268(1):91-108.
16. Goadsby PJ, Knight YE, Hoskin KL. Stimulation of the greater occipital nerve increases metabolic activity in the trigeminal nucleus caudalis and cervical dorsal horn of the cat. Pain. 1997;73(1):23-8.
17. Aramideh M, Ongerboer de Visser BW. Brainstem reflexes: electrodiagnostic techniques, physiology, normative data, and clinical applications. Muscle Nerve. 2002;26(1):14-30.
18. Kaube H, Katsarava Z, Käufer T, Diener H, Ellrich J. A new method to increase nociception specificity of the human blink reflex.Clin Neurophysiol.2000;111(3):413-6.
19. Magis D, Vigano A, Sava S, d'Elia TS, Schoenen J, Coppola G. Pearls and pitfalls: electrophysiology for primary headaches. Cephalalgia. 2013;33(8):526-39.
20. Coppola G, Abagnale C, Sebastianelli G, Goadsby PJ. Pathophysiology of cluster headache: From the trigeminovascular system to the cerebral networks. Cephalalgia. 2024;44(2):
21. Busch V, Jakob W, Juergens T, Schulte-Mattler W, Kaube H, May A. Occipital nerve blockade in chronic cluster headache patients and functional connectivity between trigeminal and occipital nerves. Cephalalgia. 2007;27(11):1206-14.