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Greater occipital nerve block in the treatment of triptan-overuse headache: A randomized comparative study

Ö. Karadaş[1] | A. Ö. Özön[2] | F. Özçelik[3] | A. Özge[4]

[1]Department of Neurology, Ankara Mevki Military Hospital, Ankara, Turkey

[2]Department of Neurology, Liv Hospital, Ankara, Turkey

[3]Department of Medical Biochemistry, Gulhane Military Medical Academy, Haydarpasa Training Hospital, Istanbul, Turkey

[4]Department of Neurology, Mersin University School of Medicine, Mersin, Turkey

Correspondence
Omer Karadas, Department of Neurology, Ankara Mevki Military Hospital, Ankara, Turkey.
Email: dromerkaradas@gmail.com

Objectives: This study aims to investigate the efficiency of a single and repeated greater occipital nerve (GON) block using lidocaine in the treatment of triptan-overuse headache (TOH), whose importance has increased lately.

Materials and methods: In the study, 105 consecutive subjects diagnosed with TOH were evaluated. The subjects were randomized into three groups. In Group 1 (n=35), only triptan was abruptly withdrawn. In Group 2 (n=35), triptan was abruptly withdrawn and single GON block was performed. In Group 3 (n=35), triptan was abruptly withdrawn and three-stage GON block was performed. All patients were injected bilaterally with a total amount of 5 cc 1% lidocaine in each stage. During follow-up, the number of headache days per month, the severity of pain (VAS), the number of triptans used, and hsCRP and IL-6 levels were recorded three times; in the pretreatment period, in the second month post-treatment, and in the fourth month post-treatment. They were then compared.

Results: There was a statistically significant difference in the post-treatment fourth month in comparison with the pretreatment period in Group 3 ($P<.05$). Compared to Group 1, the number of headache days, VAS, and decrease in triptan need in Group 3 was statistically significant compared to Group 2 ($P<.05$). Compared to pretreatment, in the fourth month post-treatment, both hsCRP and IL-6 levels were lower only in Group 3 ($P<.05$).

Conclusions: We are of the opinion that repeated GON block in addition to the discontinuation of medication has significant efficacy for TOH cases.

KEYWORDS

greater occipital nerve, medication overuse headache, migraine, occipital nerve block, triptan-overuse headache

1 | INTRODUCTION

Headaches associated with the overuse of medication taken in the attack treatment of individuals frequently suffering from headache attacks are characterized as medication overuse headaches (MOH) and their frequency is gradually increasing. Medications that may cause medication overuse headache are non-steroid anti-inflammatory drugs, acetylsalicylic acid, acetaminophen, ergotamine, triptans, caffeine-containing analgesics, and opioids. In persistent headaches associated with the overuse of these drugs, the improvement that results from drug withdrawal or reduction is an important piece of evidence. Medication overuse headache (MOH) is estimated to affect 1%–2% of society. MOH has a considerably negative effect on quality of life and varies in frequency based on gender and socioeconomic status. Depression, anxiety, and obsessive compulsive disorder are seen more frequently in patients with MOH.[1–6] MOH is a chronic headache whose frequency gradually increases, limiting daily-life activities and posing a heavy financial burden for both individuals and the country.

It has become the third most common headache after migraine and tension-type headache.[7]

The basic approach to MOH treatment is to withdraw symptomatic medication and support compliance of treatment with an appropriate prophylaxis agent. Some cases require "bridge therapy," which is effective until the prophylaxis agent starts to take effect. Bridge therapy includes interventional treatments, as well as oral steroids.[6,7] Limited studies have been carried out on the withdrawal of frequently used symptomatic medications and the long-term prognosis of different treatments administered. In long-term follow-up, a high ratio of relapses has been observed.[7,8] It has been reported that IL-6-type cytokines are mediators of pain, especially in migraines, and that IL-6 levels are significantly high in patients with chronic headache.[9–11]

In recent years, greater occipital nerve block has started to be used for the treatment of headaches.[12] It has been reported that more than half of MOH patients positively responded to greater occipital nerve (GON) block and that GON block might be effective in MOH treatment.[13] In addition to the withdrawal of triptans, the aim of this study was to characterize the efficiency of single and consecutively administered local lidocaine injection into the greater occipital nerve area and its effect on IL-6 and hsCRP levels in triptan-overuse headache.

2 | MATERIALS AND METHODS

The study enrolled patients between the ages of 18–60 who applied with headache complaints and were diagnosed with triptan-overuse headache in accordance with ICHD-3 beta criteria.[14] All patients suffered from triptan overuse only and were not taking any therapeutic prophylactic medication. Patients who were excluded from the study are as follows (Table 1).

The prospective randomized clinical trial was confirmed by the local ethical committee, and informed consent was received from all participants. A total of 115 patients were included in the study, and the study was completed with 105 patients (Figure 1). Before treatment, all subjects were followed up for a month and the number of headache days, severity of pain (VAS-visual analog scale), and number of triptans used were recorded. The subjects included in the study were divided into three groups using computer-based randomization. Groups were specified as follows: Group 1—patients who only had their triptans abruptly withdrawn and whose GON was not blocked, Group 2—patients whose triptans were abruptly withdrawn and who received single GON block, and Group 3—patients whose triptans were abruptly withdrawn and who received three-stage GON block (once a week for 3 weeks). No other acute or prophylactic treatment was administered to patients. In detoxification, the patients' triptans were abruptly withdrawn and a daily water consumption of at least 2–3 L was ensured. Patients in Group 2 and 3 were administered single- and three-stage GON, respectively, with 2.5ml of 1% lidocaine injection administered in each stage. Injections were administered rigorously by the same investigator.

The injection was administered into the GON site, 2 cm lateral and 2 cm inferior of the external occipital protuberance. Patients were asked to lie face down on the examination couch. The GON site was cleaned with an antiseptic solution. The investigator first reached the periost using a 26-G 0.45 × 13-mm needle, and then pulled the needle 1 mm back and injected lidocaine following trilateral aspiration. Each patient received a bilateral 2.5 mL injection, and local pressure was applied to the injection site for about one minute following the injection. The patients were kept under observation for half an hour to monitor the side effects that could occur following administration. The patients were asked to record the number of headache days, duration of pain, the most severe pain level, and side effects, if any, in their headache day diaries. All evaluations were made by a different investigator who was not informed of the treatment groups. The patients were evaluated in the second and fourth months post-treatment. The number of headache days per month, severity of pain (visual analog scale—VAS), and number of triptans used were recorded. In addition, the hsCRP and IL-6 levels from blood samples taken in pretreatment were measured. The levels of hsCRP were measured with latex enhanced method using Siemens Dade Behring BN II Nephelometer (Deerfield, IL, USA). IL-6 was measured using Epoch Microplate ELISA Reader (BioTec, Winooski, USA) with 1 pg/mL analytic sensitivity Human IL-6 ELISA Kit (MyBioSource, San Diego, CA, USA).

2.1 | Statistical analysis

SPSS (Statistical Package for the Social Sciences Inc; Chicago, IL, USA) 15.0 statistics software and InStat3 GraphPad software were used for all statistic analysis. G Power Program was used in power

TABLE 1 Exclusion criteria for participation in the study

Patients diagnosed with another accompanying ICHD-3 beta
History of malignancy
History of cervical or cranial surgery
Patients who received OnabotulinumtoxinA (BoNT-A) within the last 6 months
Pregnancy or lactation
Diagnosis of anemia, bleeding diathesis, and allergies to local anesthetics
Patients with neuromuscular diseases, chronic hepatic insufficiency, and diabetes mellitus
Patients using agents affecting neuromuscular functions similar to curare or aminoglycoside
Patients with uncontrolled hypertension and decompensated heart failure
Diagnosis of hypophyseal and hypothalamic dysfunction
Patients who consumed more than 500 mg/d of caffeine within the last month
Patients with major psychiatric disorders
Patients with renal insufficiency causing increased serum urea and creatinine
Patients with any inflammatory diseases* to avoid IL-6 levels from being affected

*For example, rheumatoid arthritis, Behçet disease, sarcoidosis, systemic lupus erythematosus, juvenile idiopathic arthritis, scleroderma, Polyarteritis nodosa, and Sjögren's syndrome.

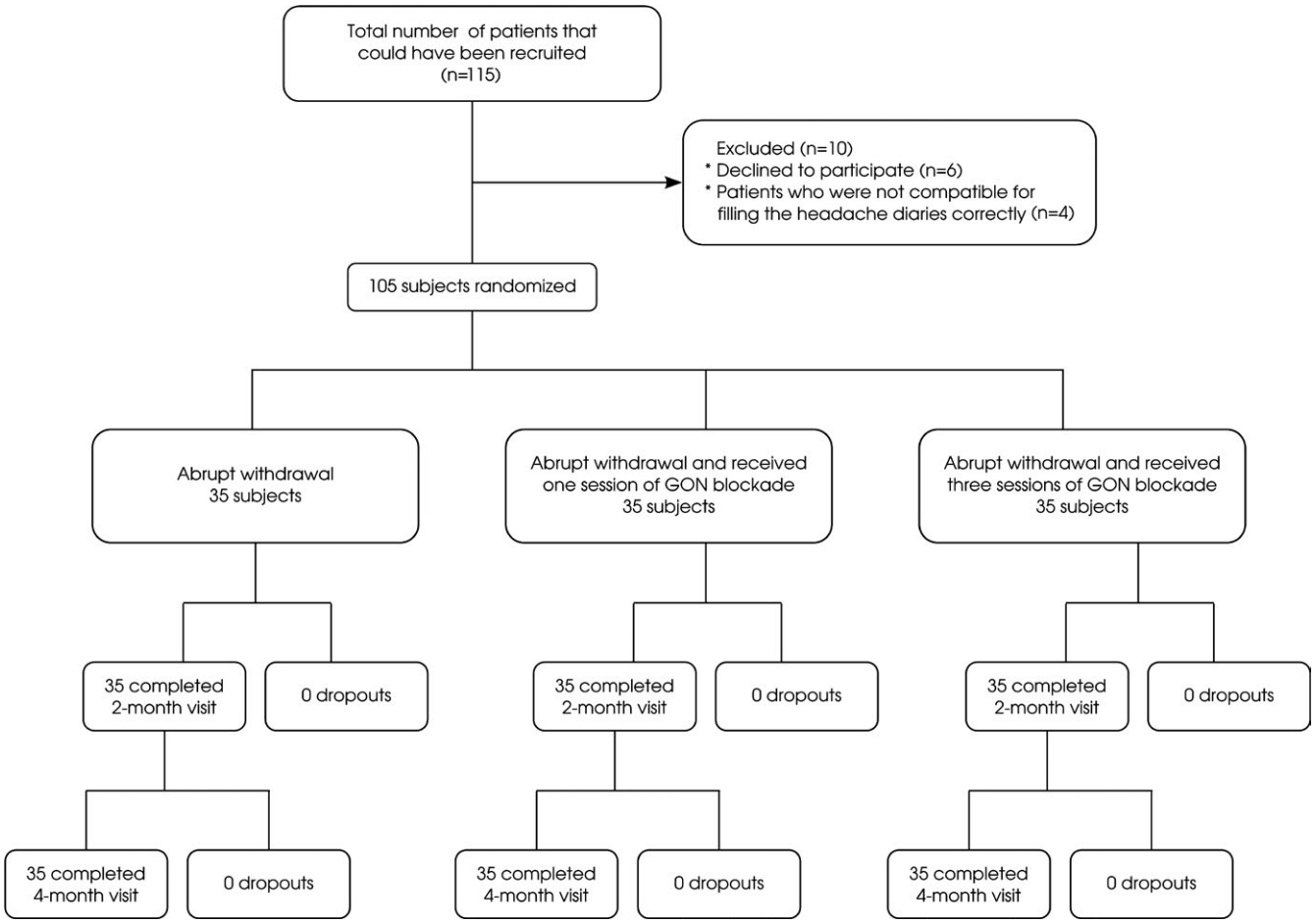


FIGURE 1 Flow diagram from recruitment to completion of the study

analysis applied to dependent groups. The repeated-measures analysis of variance for parametric data and the Friedman Test for non-parametric data were used in the analysis of the difference between dependent groups with more than two groups. One-way analysis of variance (ANOVA) for parametric and the Kruskal–Wallis test for non-parametric data were used in the analysis of the difference between independent groups whose number was greater than two. Multiple regression analysis was conducted using the selected durations of headache and medication overuse as independent variables to predict IL-6. Pearson correlation and Spearman correlation analyses were carried out, respectively, for parametric and non-parametric data.

3 | RESULTS

3.1 | Power analysis

The post hoc power calculated from the difference observed between pretreatment and post-treatment IL-6 levels in Group 3 was 0.99.

3.2 | Subject characteristics

When the characteristic specifications of subjects in the group base are evaluated, there is no statistically significant difference within the groups in terms of age, gender, BMI, waist circumference (WC), use of cigarettes and alcohol, state of illness, duration of headache, or medication overuse (Table 2).

3.3 | Evaluation of differences

When each group was evaluated in terms of the number of headache days in the pretreatment compared with the post-treatment period, only in Group 1, whose medication was reduced gradually, was there no statistical difference in the second and fourth months of post-treatment when compared to the pretreatment period ($P>.05$). On the other hand, in Group 2 and 3, the incidence of attacks decreased significantly in the post-treatment period when compared to the pretreatment period ($P<.001$). While a significant difference in the incidence of attacks in the second and fourth month post-treatment was observed in Group 3 ($P<.001$), no difference was observed in Group 2 ($P>.05$) (Table 3).

When the groups were compared to each other in terms of the number of headache days in the pretreatment compared with post-treatment period, the differences between the pretreatment clinical data of all groups were not significant ($P>.05$). While the differences observed between other groups in the second month post-treatment were not significant, the difference observed between Group 1 and

TABLE 2 Patient characteristics according to groups

	Group 1	Group 2	Group 3	*P Values
N	35	35	35	–
Male/Female	10/25	8/27	8/27	.8167[b]
Age, year	36 ± 9.4	38 ± 10.0	37 ± 9.8	.7621[a]
BMI, kg/m^2	25.9 ± 2.6	26.2 ± 3.0	26.5 ± 2.3	.6544[a]
WC, cm	85 ± 8.4	84 ± 10.7	86 ± 9.3	.6330[a]
Cigarette use, (%)	15 (43)	16 (46)	17 (49)	.8922[b]
Alcohol use, (%)	8 (23)	7 (20)	9 (26)	.8517[b]
COPD, (%)	4 (11)	6 (17)	4 (11)	.7214[b]
Primary HT, (%)	9 (26)	10 (29)	8 (23)	.8623[b]
DM, (%)	6 (17)	8 (23)	8 (23)	.7963[b]
Hyperlipidemia, (%)	7 (20)	10 (29)	9 (26)	.7016[b]
Headache duration, year	14.7 ± 6.5	15.3 ± 7.6	14.6 ± 8.3	.9139[a]
DTO, Year	7.5 ± 2.9	7.9 ± 2.8	7.4 ± 3.8	.8250[a]

BMI, Body mass index; WC, Waist circumference; COPD, Chronic obstructive pulmonary disease; HT, Hypertension; DM, Diabetes mellitus; DTO, Duration of triptan overuse.
*Comparison between all groups.
[a]One-way analysis of variance (ANOVA), [b]Kruskal–Wallis test (Nonparametric ANOVA).

Group 3 data was significant (*P*<.01). There were also significant differences between Group 1 and 3, and Group 2 and Group 3 in the fourth month post-treatment (*P*<.01) (Table 3).

When the groups were evaluated in terms of severity of pain in the pretreatment compared with post-treatment period, while there was no significant difference in Group 1, it was remarkable that there was a significant decrease in the severity of attacks when Group 2 and Group 3 data in the second and fourth months of pre- and post-treatment were compared (*P*<.001). When the groups were compared to each other in terms of severity of pain in the pretreatment compared to the post-treatment period, the difference observed between the clinical data of Group 1, Group 2, and Group 3 in both the second and fourth month of post-treatment was statistically significant (*P*<.01) (Table 3).

When the groups were evaluated in terms of the number of triptans used in the pretreatment compared with post-treatment period, while there was no significant difference in Group 1, there was a significant difference in Group 2 and Group 3 (*P*<.0001). While there was only a statistically significant difference in the pretreatment and post-treatment fourth month data of Group 2 (*P*<.001), there was a statistically significant difference in the data of pretreatment and second and fourth month post-treatment for Group 3 (*P*<.05). When the groups were compared to each other in terms of number of triptan used, the difference observed between the clinical data of Group 1, Group 2, and Group 3 in both the second and fourth months of post-treatment was statistically significant (*P*<.01). Other statistical comparisons were as shown in Table 3.

When the groups were evaluated in terms of hsCRP level studies as a marker of inflammation in the pretreatment compared with the post-treatment period, while no difference in Group 1 and Group 2 was detected, the hsCRP levels of Group 3 were lower in the fourth month when compared to the pretreatment period (*P*<.05) (Table 3).

When the groups were evaluated in terms of IL-6 levels in the pretreatment compared to post-treatment period, there was a statistically significant difference in Group 1 and Group 2 (*P*<.001) (Table 3). While a difference was observed between the data in the pretreatment and post-treatment fourth month in Group 2, there was a difference between data in the pretreatment and post-treatment second and fourth months in Group 3 (*P*<.01). Other comparisons were as shown in Figure 2. In the fourth month post-treatment, only the IL-6 levels of Group 3 were significantly lower in comparison with the IL-6 levels of Group 1 (*P*<.05).

3.4 | Correlation studies

It was observed that pretreatment IL-6 levels had a lower positive correlation with the duration of medication overuse (duration of triptan overuse—DTO) and a perfect positive correlation with headache duration (Figure 3). Likewise, IL-6 levels in the second and fourth months of post-treatment showed low correlation with DTO (respectively, Spearman r=0.352 *P*=.0002 and Spearman r:0.409 *P*<.0001). Once again, IL-6 levels in the second and fourth months post-treatment showed perfect correlation with headache duration (respectively, Pearson r: 0.627 *P*<.0001 and Pearson r: 0.617, *P*<.0001).

In multiple regression analysis carried out to determine the cause–effect relation between headache duration and DTO (thought to be at the back of IL-6 levels), examine its severity, and estimate IL-6 levels with the help of these variables, it was observed that 45% of IL-6 levels were affected by these (Figure 3). It was observed that age showed an average correlation with medication overuse duration and IL-6 levels and a perfect correlation with headache duration (Figure 4).

4 | DISCUSSION

This randomized clinical trial was evaluated with a 4-month follow-up. In terms of abrupt withdrawal of medication for triptan-overuse

TABLE 3 Comparison of the number of headache days, VAS, the number of triptan, IL-6, and hsCRP levels according to treatment options

	Group 1	Group 2	Group 3	*P Value	Comparison G1-G2, G1-G3, G2-G3
NHD					
Pretreatment (A)	18.1 ± 3.8	19.1 ± 3.8	19.7 ± 3.3	.1680[a]	–
Post-treatment 2nd month (B)	16.9 ± 3.7	15.9 ± 3.9	14.1 ± 4.6	. 0051[a]	>0.05, <0.01, >0.05
Post-treatment 4th month (C)	16.9 ± 4.3	14.8 ± 4.7	9.7 ± 4.5	<.0001[a]	>0.05, <0.001, <0.001
*P values	0.0649[c]	<0.0001[c]	<0.0001[c]		
Comparison (A-B, A-C, B-C)		<0.001, <0.001, >0.05	<0.001, <0.001, <0.001		
VAS					
Pretreatment (A)	87.9 ± 7.6	89.7 ± 7.4	87.9 ± 8.8	.5025[a]	–
Post-treatment 2nd month (B)	83.4 ± 12.0	82.6 ± 10.5	67.3 ± 17.9	<.0001[a]	>0.05, <0.001, <0.001
Post-treatment 4th month (C)	83.6 ± 10.0	77.1 ± 14.5	56.7 ± 15.7	<.0001[a]	>0.05, <0.001, <0.001
*P value	.0508[c]	<.0001[c]	<.0001[c]		
Comparison (A-B, A-C, B-C)		<0.01, <0.001, <0.05	<0.001, <0.001, <0.001		
NT					
Pretreatment (A)	15.1 ± 3.4	14.7 ± 3,3	15.3 ± 3.7	.7802[b]	–
Post-treatment 2nd month (B)	13.6 ± 4.0	12.0 ± 2.8	10.1 ± 2.9	.0005[b]	>0.05, <0.001, >0.05
Post-treatment 4th month (C)	13.3 ± 4.1	10.6 ± 3.9	6.8 ± 3.1	<.0001[b]	>0.05, <0.001, <0.01
*P values	.2952[d]	<.0001[d]	<.0001[d]		
Comparison (A-B, A-C, B-C)		>0.05, <0.001, >0.05	<0.05, <0.001, <0.001		
hsCRP, mg/L					
Pretreatment (A)	3.79 ± 1.84	3.89 ± 2.22	4.06 ± 2.20	.8662[a]	–
Post-treatment 2nd month (B)	3.80 ± 2.05	3.84 ± 2.52	3.70 ± 1.47	.9557[a]	–
Post-treatment 4th month (C)	3.52 ± 1.82	3.53 ± 1.81	3.25 ± 1.57	.7471[a]	–
*P values	.6162[c]	.5341[c]	.0363[c]		
Comparison (A-B, A-C, B-C)			>0.05, <0.05, >0.05		
IL-6, pg/mL					
Pretreatment (A)	15.5 ± 9.2	15.3 ± 8.6	16.2 ± 9.1	.9121[a]	–
Post-treatment 2nd month (B)	13.8 ± 8.8	14.1 ± 8.5	13.2 ± 7.4	. 9090[a]	–
Post-treatment 4th month (C)	14.4 ± 9.5	12.6 ± 6.9	10.0 ± 4.4	.0415[a]	>0.05, <0.05, >0.05
*P values	.1230[c]	.0010[c]	<.0001[c]		
Comparison (A-B, A-C, B-C)		>0.05, <0.001, >0.05	<0.01, <0.001, <0.01		

NHD, the number of headache days; NT, number of triptan used; VAS, visual analog scale.
*Comparison between all groups with post-test, [a]One-way analysis of variance (ANOVA), [b]Kruskal–Wallis test (Nonparametric ANOVA), [c]Repeated-measures ANOVA, dFriedman test.

headache (TOH) patients, single- and three-stage GON blocks with lidocaine injection following abrupt withdrawal of medication were found to be effective for migraine attack frequency, attack duration (hour), and decreased severity of pain in the post-treatment period when compared to the pretreatment period. The efficiency of repeated GON block administration revealed better results than single GON block administration. In the fourth month, IL-6 levels were significantly lower in Group 3 compared to Group 1 who did not receive GON blocks. In recent studies on several painful cases such as primary headaches, particularly migraine, and medication overuse headache (MOH), emphasis has been lain on the importance of the greater occipital nerve and the development of treatment strategies.

GON block is a promising treatment for TOH treatment. However, the practice techniques and criteria are not clear enough to determine its area of use. There are no available placebo-controlled GON block studies on TOH, which is frequently used in the asymptomatic treatment of migraines. Recent placebo-controlled studies focus on the efficiency of GON blocks for migraines excluding MOH and TOH. In a placebo-controlled multicenter study, the efficiency of repeated GON block in treatment was indicated in chronic migraine treatment without MOH.[15] In another placebo-controlled multicenter study, single GON block was administered to patients experiencing chronic migraine without MOH and the short-term results were evaluated. A different low-dose local anesthetic was given to the placebo group. In this study, efficiency was defined as a decrease of 50% or more in the

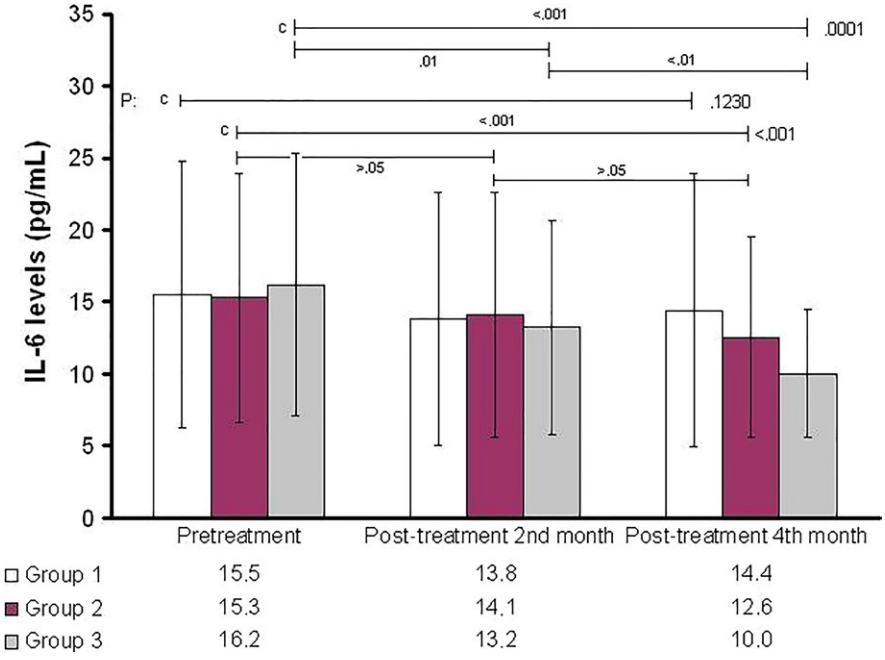
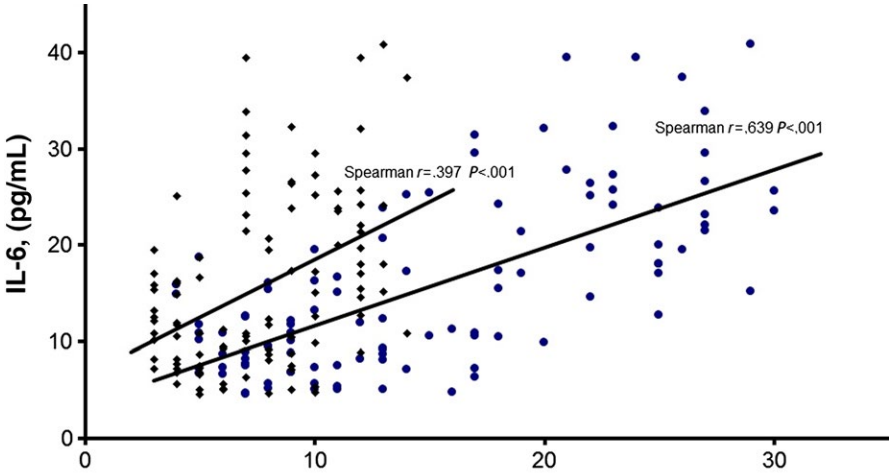


FIGURE 2 Graphic showing statistical comparison and results of age-based IL-6 levels in pretreatment, post-treatment second and fourth months



[IL-6 (pg/mL)] = 3.449 + 0.7961*[Headache duration (year)] + 0.04724*[Duration of triptan overuse (year)]

R-squared: 0.4574, adjusted *R*-squared: 0.4468, Multiple *R*: 0.6763, *F*: 42.994, *P*< .0001

Variable	Coefficient	SE	95% CI	*t* ratio	*P* value
(constant)	3.449	1.733	0.006563 to 6.892	1.990	0.0493
Headache duration	0.7961	0.111	0.5757 to 1.016	7.174	<0.0001
Duration of triptan overuse	0.04724	0.2595	−0.4682 to 0.5626	0.1820	0.8559

FIGURE 3 Spearman correlation analysis between duration of headache with IL-6 and duration of triptan overuse. In addition, multiple regression analysis predicting IL-6 levels from duration of headache and triptan overuse as independent variables

number of migraine headache days. At the end of the study, the efficiency of the treatment group compared with the placebo group could not be indicated.[16] In our study, single and repeated GON blocks were administered to patients with TOH developed as a basis of migraine and were observed to be effective in the treatment. It was observed that repeated local lidocaine injection into GON sites resulted in a better response to the treatment.

The efficiency of GON blocks in MOH and TOH treatments was studied in non-placebo-controlled studies. Afridi et al. administered GON blocks to 31 patients with MOH developed in migraine basis and found GON blocks to be effective for 20 patients.[17] In Tobin et al.'s study, the achievement drive of GON blocks in the treatment of MOH developed on a migraine basis was found to be lower compared to the achievement drive of GON blocks administered in the treatment of migraine not accompanied by MOH.[18] Additionally, GON block was found to be effective in the treatment of two subjects with TOH developed on a cluster headache basis.[18] In our study, the administration of repeated GON blocks within the period when triptan was discontinued in TOH treatment was found to be quite effective at decreasing headaches. These different results obtained from the studies arise from the difference of GON block techniques and administration criteria.

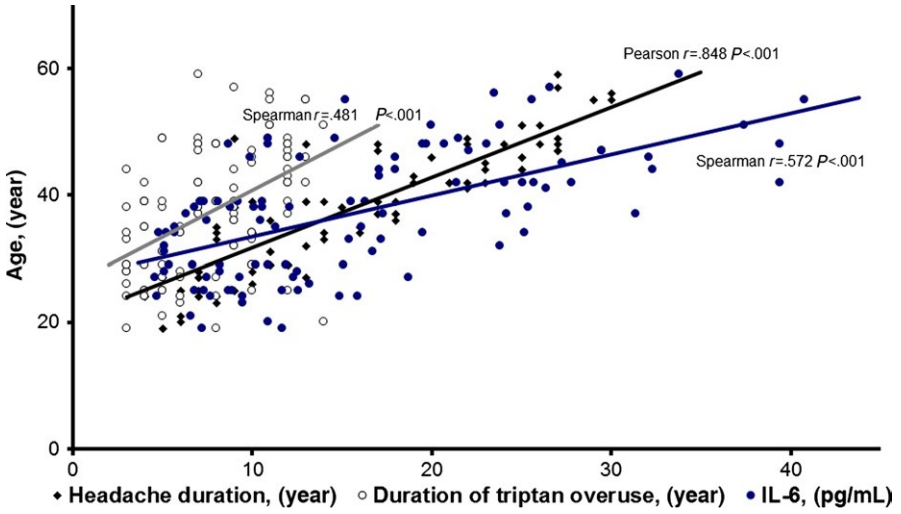


FIGURE 4 Pearson and Spearman correlation graphic made for age and pretreatment IL-6 levels, duration of headache, and triptan overuse

In past studies, it has been stated that cytokines such as IL-6 and TNF-α are pain mediators in neurovascular inflammation. Fidan et al. found that the IL-6 levels of migraine patients were higher in comparison with the control group in their study. IL-6 is a pro-inflammatory cytokine released from T cells and macrophages as the stimulant of immune response. It is known to cause inflammation in the event of infection and trauma. In addition, this cytokine, which is an important mediator of fever and acute phase response and induces PGE2 synthesis by passing the blood–brain barrier easily, has been confirmed to be formed also by the smooth muscles cells of numerous blood vessels.[9,10,19,20] As a result of our study, the possible mechanism of observed decrease in the incidence of headache in proportion with IL-6 levels following GON block administration can be attributed to decrease in inflammation developed in association with IL-6 levels following GON block.

The trigeminal nerve carries cranium-based pain sensation. The trigeminocervical complex also has connections with the salivatorius superior and upper cervical nerves, which are always in communication with superior centers.[21] In an experimental study, it was observed that greater occipital nerve stimulation affects the ipsilateral trigeminal nerve first branch (V1). These results showed that extensions of cervical nociceptive neurons cause synapses in trigeminal nuclei.[22] In our study's patient evaluations, GON block was bilaterally administered because headaches were sometimes left-sided, sometimes right-sided, and sometimes generalized. It is observed that the duration of clinical recovery following GON blocks with lidocaine continues longer than the half-life of lidocaine. This may result from a regulation in nociceptive pathways associated with the trigeminocervical complex connected to upper cervical nerves. It seems that it is possible to prolong this effect and get a longer response through repeated GON block injections.

In conclusion, GON block administration with local lidocaine following discontinuation of acute treatment has been found to be an effective method in TOH treatment. It was determined that repeated GON block with local lidocaine is superior to single GON block administration. At the endpoint of the study, a decrease in IL-6 levels was observed in repeated GON block administration. In addition, no serious adverse reaction that may lead to suspension of the study was observed during injection administrations. This suggests the safety and tolerability of repeated GON block with lidocaine in preventive migraine treatment. The most important limitation of this study is the lack of placebo groups.

The efficiency of local anesthetic injections administered in the treatment of primary headaches and MOH developed on the basis of these headaches was found to differ from each other. Those differences can be due to factors including headache type, presence of mixed headache, local anesthetic type, local anesthetic dose, pharmacologic combination, study design, administration method, and number of administrations. In order to completely determine the efficiency and power of GON block in TOH treatment, we need to conduct randomized, double-blind, placebo-controlled, and long-term follow-up studies featuring combinations of local anesthetics at different doses with local anesthetics or with steroids and repeated numbers of injections.

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CONFLICT OF INTEREST

None declared.

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