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Comparison of outcomes of transnasal sphenopalatine ganglion and ultrasound-guided proximal greater occipital nerve blockades in chronic migraine

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Abstract

Background & Objective: A need exists for prophylactic treatment options for chronic migraine. Our aim was to evaluate and compare the effect of greater occipital nerve (GON) and transnasal sphenopalatine ganglion (SPG) blockade on headache days, responder rate, attack severity, attack frequency, and medication overuse in patients with chronic migraine. *Methods:* This was a retrospective study. The GON blockade was performed at the proximal level under ultrasound guidance with 1.5 cc 0.5% bupivacaine, and the SPG blockade was performed transnasally with 0.5 cc 0.5% bupivacaine applied for 30 minutes with swab sticks. Patients who completed bilateral blocks applied in four weekly sessions were included in the analysis. *Results:* Seventy patients (GON=37, SPG=33) were included in the study. Both groups showed a significant improvement in the number of days with headache, severity of attacks, and frequency of attacks at the first- and third-month follow-up visits compared to the baseline ($p<0.001$). Responder rates were similar at the first- and third-month follow-up visits ($r= 3.707$, $p=0.054$; $r=0.071$, $p=0.790$, respectively). At the third-month follow-up, the prevalence of medication overuse decreased from 78% to 13% in the GON group and from 57% to 9% in the SPG group, and these differences were statistically significant ($p<0.001$ for both groups). No significant difference was noted in efficacy between the treatment groups ($p=0.714$). No significant adverse effects occurred in either group.
Conclusion: Both proximal GON blockade and minimally invasive SPG blockade are effective and safe options for prophylaxis in patients with chronic migraine.

Keywords: chronic migraine; greater occipital nerve; sphenopalatine ganglion; nerve blockade

INTRODUCTION

Chronic migraine negatively affects psychological health, financial status, general health, and quality of life[1] and has an estimated prevalence of 1.4–2.2%.[2] Topiramate, onabotulinum toxin A, and anti-calcitonin gene-related peptide monoclonal antibodies are recommended prophylactic treatment options for chronic migraine.[3] Among the percutaneous interventional treatments available for chronic migraine prophylaxis, the administration of onabotulinum toxin A is strongly recommended, whereas support for greater occipital nerve (GON) and sphenopalatine ganglion (SPG) blockade is weak.[4] The need for specific and easily tolerated prophylactic treatment options continues in patients with chronic migraine.[5]

Trigeminocervical hypersensitization and cortical hyperexcitability are possibly responsible for the pathophysiology of chronic migraine.[6,7] The effect of GON blockade on the inhibition of the afferent pathway of trigeminocervical sensitization has been emphasized.[8] Recently, GON blockade has been demonstrated to reduce plasma levels of calcitonin gene-associated peptide in the interictal migraine period.[9] Gul

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et al.[10] revealed that the application of a GON blockade once a week for four sessions to chronic migraine sufferers reduced the number of days with headache and the attack severity compared to placebo in the short term. Pingree *et al*.[11] showed that an ultrasound-controlled proximal GON blockade could safely achieve one month of clinical efficacy in chronic migraine.

The release of inflammatory mediators due to vasodilation in the cranial blood vessels causes headache and has been thought to be inhibited by SPG blockade. Central sensitization in the trigeminal nucleus can also be prevented by this inhibition.[12] Some headache specialists have stated that SPG blockade is the most beneficial option for patients with chronic migraine; however, the lack of evidence-based protocols for SPG blockade has resulted in reduced preference for this procedure.[13] Some evidence indicates that the effectiveness of transnasal SPG blockade in patients with chronic migraine is limited to 24 hours, making this a short-term treatment option.[14] Studies in the literature showing the prophylactic efficacy of SPG blockade in patients with chronic migraine have been small and uncontrolled.[15-17]

The first aim of our study was to compare the effects of ultrasound-controlled proximal GON blockade with transnasal SPG blockade, conducted for four sessions once a week, on the number of days with headache in a month in patients with chronic migraine. The second aim was to compare responder rate, severity of attacks, number of attacks, duration of attacks, medication overuse, and conversion to low-frequency episodic migraine between the GON and SPG blockade groups.

METHODS

Study design and ethics

This retrospective analysis was performed between March 2019 and March 2022 at two tertiary hospitals after obtaining approval from the local Ethics Committee (no. 2022/3679; date: March 4, 2022). The present study was conducted in accordance with the Declaration of Helsinki.

Participants

Our file review identified 80 patients who underwent an interventional procedure after a diagnosis of chronic migraine according to the criteria of the International Classification of Headache Disorders, third edition (beta version). After inclusion and exclusion criteria (Table 1) were applied, 70 patients were included in the study (Figure 1).

Variables and outcomes

Demographic data obtained from file reviews included the age at migraine onset (years), migraine duration (years) in the migraine history, psychiatric disease history, presence of medication overuse, migraine characteristics at baseline (one month before the procedure), and review visits one and three months after the end of treatment (days with headache/month, headache attack numbers/month, average attack duration, and average attack severity information of the patients).

Patients who had a 50% or more reduction in the number of days with headache in a month compared to baseline values were considered responders.[3]

Table 1: Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
1. Patients who had chronic migraine for at least six months 2. Patients who attended all four sessions of their procedures 3. Patients who maintained a headache diary for at least one month before the procedure 4. Patients reviewed at the headache outpatient clinic one and three months after the last procedure with a completed headache diary	1. Patients who had a history of trauma or surgery involving the head and neck area with any etiology 2. Patients who had any anatomical deformation that disrupted the head and neck contour 3. Patients who had received an injection of onabotulinum toxin for migraine in the last 12 months or had undergone any interventional procedure on the greater occipital nerve, sphenopalatine ganglion, or supraorbital nerve 4. Patients with a history of severe psychiatric illness 5. Patients who had undergone prophylactic pharmacological agent changes three months before and during the follow-up period

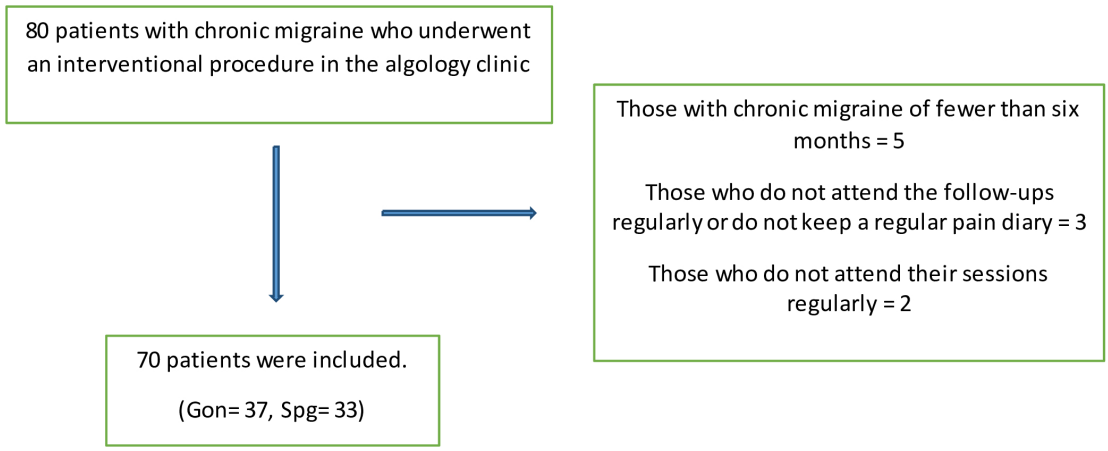

Figure 1. Flow chart

Medication overuse in patients was defined as nonsteroidal anti-inflammatory drug (NSAID) use at least 15 days a month, or triptan with or without NSAID use at least 10 days a month.

The rate of transformation to low-frequency episodic migraine in the groups was evaluated by comparing the number of monthly headache days within the third month to the monthly migraine days at baseline.

Intervention

Onabotulinum toxin is an approved interventional procedure in chronic migraine prophylaxis. However, for economic reasons, the toxin was challenging to obtain. Our initial approach in our patients was to perform an ultrasound-controlled proximal GON blockade. However, transnasal SPG blockade was performed when the ultrasound device was not fully functional or unavailable, and in patients with needle phobia. The same researcher performed all applications.

The SPG blockade consisted of the application of swab sticks impregnated with 0.5 cc 0.5% bupivacaine to both nostrils bilaterally for 30 minutes for four sessions once a week.

The GON blockade was implemented as described previously[18] using a 12 MHz linear transducer (Siemens ACUSON S2000 and Mindray DC-60) with a sterile cover. Bupivacaine 0.5% (1.5 cc) was injected into each GON with a 21-gauge 1.5 inch needle once weekly for four sessions.

Statistics

Categorical variables were presented as numbers and percentages, normally distributed numerical variables as means (±standard deviation), and non-normally distributed numerical variables as medians (25–75% percentiles). Chi-square or Fisher exact tests were used for analysis of differences between the groups in terms of gender, marital status, whether the headache was accompanied by autonomic symptoms, and the presence of GON tenderness on palpation. The relationship between pre-procedure migraine onset age (years), migraine diagnosis duration (years), days with headache/month, number of attacks/month, mean attack severity (determined by a VAS score), and mean attack duration (hours) between the groups were analyzed using the Mann-Whitney U test.

The changes in migraine characteristics (number of days with headache/month, number of attacks/month, mean pain intensity, and mean attack duration) at the first- and third-month visits compared to the baseline values were analyzed using the Friedman test. The Wilcoxon rank-sum test was performed to compare repetitive measurements. The Bonferroni correction was used to avoid possible type 1 errors.

Comparison of the number of days with headache/month, number of attacks/month, attack severity (determined with a 0-100 mm visual analog scale [VAS]), attack duration (hours) parameters between the groups at follow-up visits and the percent change in those parameters from baseline at the follow-up visits were analyzed using the Mann-Whitney U test.

The chi-square and Fisher's exact tests determined whether a difference existed between the groups regarding medication overuse at baseline and the third-month visit. The relationship between the presence of medication overuse

before the procedure and after the third month was analyzed using the McNemar test.

The chi-square test was used to determine whether a difference existed between the groups for the rates of transformation into low-frequency episodic migraine at the third-month visit and whether the responder rates differed between the first- and third-month visits. The number and rates of adverse effects and complications were also recorded.

RESULTS

Seventy patients (GON=37, SPG=33) were evaluated in the study. The GON and SPG groups did not differ significantly in terms of gender, marital status, accompanying autonomic symptoms, or the presence of GON sensitivity ($p = 0.883, 0.863, 0.395$, and 0.394, respectively). The mean age was 40.22 (±10.57) years for the GON group and 40.51 (±10.73) years for the SPG group, with no significant difference between the groups (p= 0.729).

Group comparisons in terms of migraine characteristics before the procedure are presented in Table 2. Medication overuse before the procedure occurred in 29 (78.38%) patients in the GON group and 19 (57.57%) in the SPG group, with no significant difference between the groups (r= 3.503, p= 0.061).

There was a statistically significant difference in migraine headache characteristics at follow-up visits compared to baseline in both groups (Tables 3 and 4, Figures 2 and 3).

No statistically significant difference was detected between the groups in terms of migraine characteristics between the first and third months after treatment (Table 5 and Figure 4).

No statistically significant difference was detected between the groups for the percentage changes in migraine characteristics at follow-up visits, except for the attack duration (Table 6).

The responder rates at the first-month and third-month visits were 63.64% (21) and 72.97% (27), respectively, in the SPG group and 83.78% (31) and 75.76% (27), respectively, in the GON group. No statistically significant difference was detected between the groups at the first- and third-month follow-up visits (r= 3.707, p= 0.054; r= 0.071, p= 0.790, respectively).

Medication overuse was present in 5 (13.51%) patients in the GON group at the third-month visit and in 3 (9.09%) patients in the SPG group. The presence of medication overuse was statistically reduced at the third-month visit compared to baseline in both within-group assessments (p <0.001). No statistically significant difference was determined between the groups (r= 0.337, p= 0.714).

At the third-month visit, 25 (67.57%) patients in the GON group and 21 (63.64%) patients in the SPG group were transformed into low-frequency episodic migraine. No statistically significant difference was evident between the episodic low-frequency, episodic high-frequency, or chronic migraine rates of the groups (p= 0.942).

Evaluation of side effects and complications revealed a history of a moderate-to-severe migraine attack after the procedure in 11 (29.73%) patients in the GON group and in 7 (20.23%) patients in the SPG group. In the GON group, the dizziness occurred in 7 (18.92%) patients and regressed after an extended rest period; 3 (8.11%) patients developed moderate-to-severe local pain lasting approximately one day in the first session; one patient had a vertigo attack that required parenteral metoclopramide and dimenhydrinate treatment. In the SPG group, 29 (87.88%) patients had lacrimation that did not exceed the procedure time and did not cause severe discomfort in all sessions, and 7 (21.21%) patients had a trace amount of bleeding.

Table 2: Comparison of the baseline migraine histories and characteristics of the treatment groups

Baseline variables	Median (25–75% percentiles)		P-value
	GON Group	SPG Group	
Age at migraine diagnosis	23.5 (19.25–34.50)	25.0 (20.50–37.50)	0.613
Chronic migraine duration (month)	10.5 (8.0–117.5)	12.61 (7.5–14.0)	0.503
Number of headache days in a month	23.0 (16.0–30.0)	26.0 (22.0–30.0)	0.232
Headache frequency in a month	15.50 (8.0–30.0)	25.0 (13.5–30.0)	0.102
Mean headache attack duration (hour)	22.0 (10.0–58.5)	15.0 (7.0–45.0)	0.260
Mean pain severity (0–100 mm)	90.0 (80.0–97.5)	90.0 (82.5–95.0)	0.940

Table 3: Migraine headache characteristics at baseline and post-intervention in the GON group

Variables	Median (25–75% percentiles	95%C.I.	*P-value*
Number of headache days in a month			
baseline	25.0 (16.0–30.0)	21.1–25.38	
1st month	4.0 (2.0–10.5)	4.5–9.6	<0.001
3rd month	4.0 (1.5–12.0)	4.46–10.35	
Mean pain severity (0–100 mm)			
baseline	90.0 (80.0–95.0)	86.33–91.77	
1st month	50.0 (22.5–70.0)	40.36–59.91	<0.001
3rd month	50.0 (20.0–80.0)	36.75–58.65	
Headache frequency in a month			
baseline	16.0 (8.0–30.0)	14.77–21.34	
1st month	4.0 (2.0–8.5)	3.87–8.18	<0.001
3rd month	3.0 (2.0–8.5)	3.72–9.03	
Mean headache attack duration (hours)			
baseline	24.0 (10.0–57.0)	22.79–40.39	
1st month	5.0 (3.0–12.0)	5.99–15.73	<0.001
3rd month	5.0 (2.0–15.0)	6.21–16.81	

DISCUSSION

The findings of this study revealed improvements in the number of days with headache, the severity of attacks, frequency of attacks, and prevalence of medication overuse without any severe adverse effects or complications in both the GON and SPG groups. Responder rates and conversions to episodic migraine were similar in both groups.

A similar significant improvement was also noted in the number of days with headache, attack severity, and attack frequency compared to baseline at the first- and third-month visits in both

Table 4: Migraine headache characteristics at baseline and post-intervention in the SPG group

Variables	Median (25%–75% percentiles)	95%C.I.	*P-value*
Number of headache days in a month			
baseline	26.0 (20.0–30.0)	22.58–26.75	
1st month	6.0 (7.43–15.96)	7.43–15.96	<0.001
3rd month	4.0 (2.0–13.5)	5.57–13.46	
Mean pain severity (0–100 mm)			
baseline	90.0 (82.5–95.0)	84.81–91.55	
1st month	60.0 (40.0–90.0)	48.71–70.38	<0.001
3rd month	60.0 (35.0–82.5)	47.09–67.75	
Headache frequency in a month			
baseline	25.0 (13.5–30.0)	18.59–24.86	
1st month	5.0 (2.0–22.0)	6.18–14.06	<0.001
3rd month	4.0 (2.0–10.0)	4.84–12.49	
Mean headache attack duration (hours)			
baseline	15.0 (7.0–45.0)	16.31–33.44	
1st month	8.0 (4.0–13.5)	8.25–22.35	<0.001
3rd month	6.0 (4.0–13.5)	7.54–21.67	

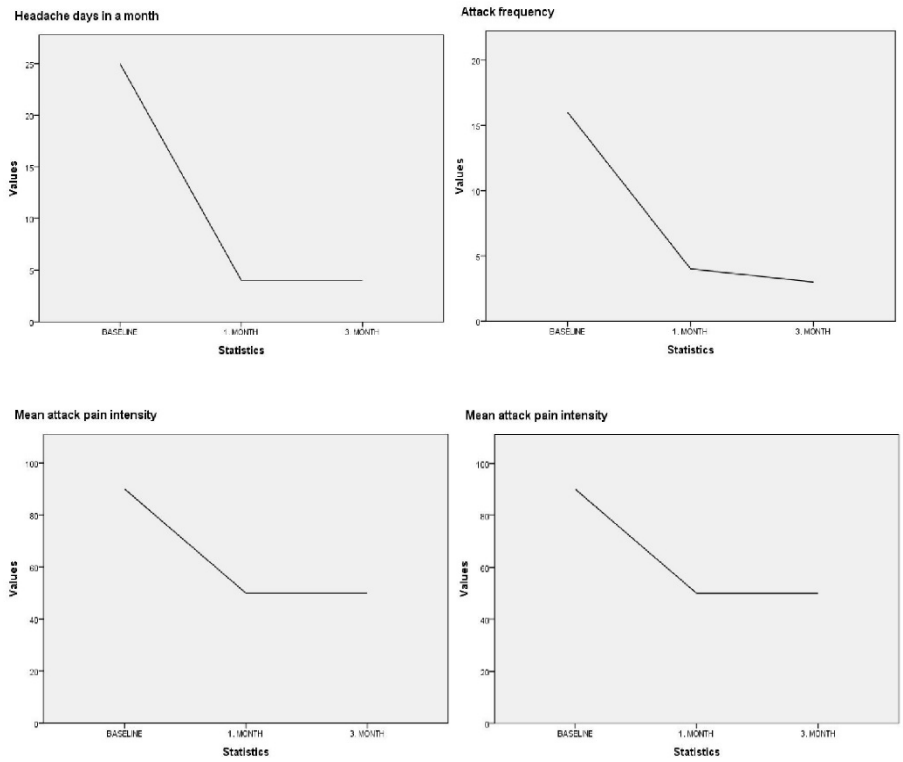

Figure 2. Migraine headache characteristics at baseline and post-intervention in the GON group

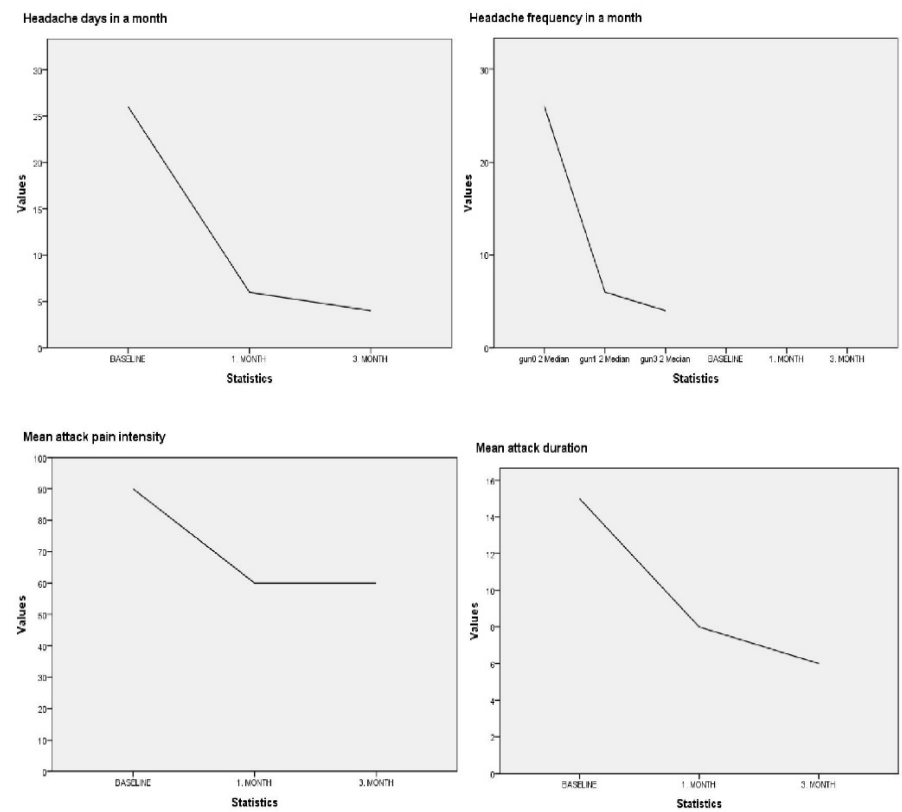

Figure 3. Migraine headache characteristics at baseline and post-intervention in the SPG group

Table 5: Comparison of migraine characteristics of the groups at the follow-up visits

Migraine characteristics	Follow-up visits	Median (25–75% percentiles)		P-value
		Group GON	Group SPG	
Number of headache days in a month	1st month	4.0 (2.0–10.75)	6.0 (2.0–25.5)	0.306
	3rd month	4.0 (2.0–13.0)	4.0 (2.0–13.5)	0.553
Headache frequency in a month	1st month	4.0 (2.0–9.25)	5.0 (2.0–22.0)	0.372
	3rd month	3.5 (2.0–9.25)	4.0 (2.0–10.0)	0.609
Mean headache attack duration (hour)	1st month	5.5 (2.25–16.5)	8.0 (4.0–13.5)	0.229
	3rd month	5.5 (2.25–16.5)	6.0 (4.0–13.5)	0.471
Mean pain severity (0–100 mm)	1st month	50.0 (26.25–70.0)	60.0 (40.0–90.0)	0.174
	3rd month	50.0 (20.0–80.0)	60.0 (35.0–82.5)	0.219

groups. We also concluded that although a clinical response was obtained in the majority of patients in both groups, the responder rates were similar. The available literature, which includes randomized, double-blind, and placebo-controlled studies[10,19,20], demonstrates the effectiveness of distal GON blockade in chronic migraine prophylaxis, but no placebo-controlled studies have been published on proximal GON blockade. However, in line with our study findings, many studies have indicated the effectiveness of proximal GON blockade on the number of days with headache, attack severity, and attack frequency over short durations in patients with chronic migraine.[9,11,21-24] Few studies evaluated the effects of SPG blockade on chronic migraine prophylaxis. Additional *et al*.[15] applied transnasal SPG blockade to a patient with chronic migraine and determined that pain relief continued throughout a 28-day follow-up, and the clinical improvement persisted for one year with recurrent blockades (15). Cady *et al*.[25] evaluated the prophylactic effect of a transnasal sphenopalatine ganglion blockade applied with 0.3 cc of 0.5 bupivacaine using a Tx360® nasal applicator twice a week for six weeks. Although bupivacaine was not statistically superior to placebo, a clinically significant improvement was obtained in the number of days with headaches at the first visit in patients who were administered bupivacaine. Bupivacaine showed a non-significant trend to superiority to placebo, and the authors attributed the lack of statistical significance to an underpowered study.[25] Tepe and Tertemiz[17] evaluated the clinical results of bilateral transnasal SPG blockade lasting for 30 minutes and applied every two weeks in four sessions with a swab stick impregnated with 1 cc 0.5% bupivacaine. At the end of the two-month follow-up, an improvement was observed in the number of days with pain, frequency of migraine attacks, severity of attacks, and duration of attacks.[17] These studies revealed that application doses and intervals of both GON blockades and SPG blockades can differ. To the best of our knowledge, no study in the literature has evaluated the relative superiority of different doses and intervals of these blockades in migraine treatment.

In the present study, a comparison of the third-month visit to the baseline revealed a statistically significant decrease in the mean attack severity in both groups. The reduction rates were 35% and 28% for the GON and SPG groups, respectively. Maizels *et al*.[26] reported a 53% reduction in pain intensity in the acute treatment of migraine attacks with intranasal lidocaine administration compared to placebo. Cady *et al*.[25] reported that repeated transnasal SPG blockade has a significant improvement in mean pain intensity at short and medium-period follow-up visits. But the improvement was not over the placebo. To the best of our knowledge, no cut-off value has been established for the change in the pain intensity parameter that determines the superiority of a prophylactic migraine treatment over placebo. The literature shows that the GON blockade has a short-term efficacy compared to placebo in chronic migraine prophylaxis.[10,19,20] In the present study, we found no statistical difference between the treatment groups, suggesting that SPG blockade is also more effective than placebo.

At the third-month follow-up, we found that baseline medication overuse decreased from 78% to 13% in the GON group and from 57% to 9% in the SPG group. Consistent with our findings, the literature shows that medication overuse can be significantly reduced in both the early[24-27] and medium periods[21] with the GON blockade in patients with chronic migraine. Cady *et al*.[25]

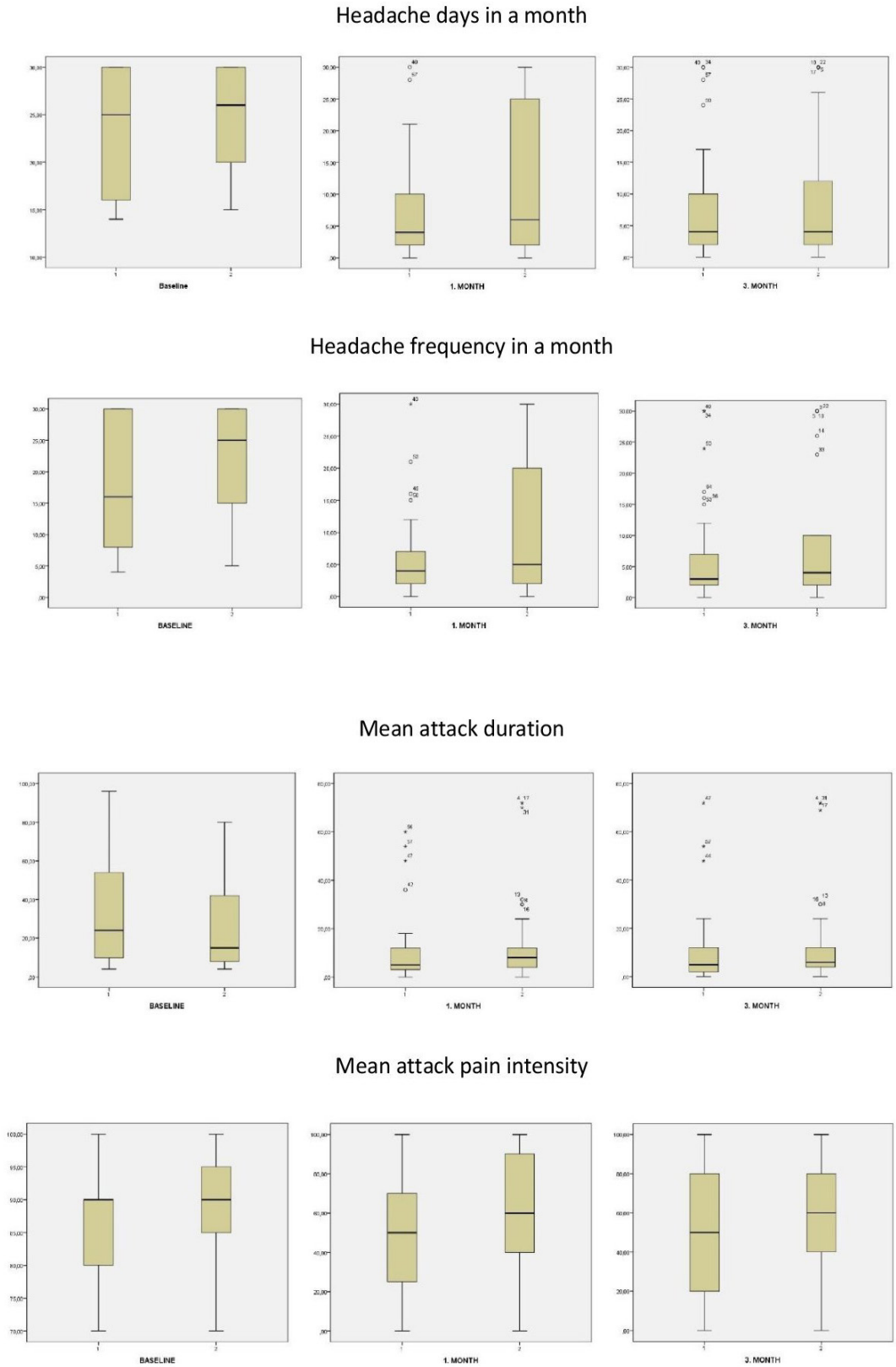

Figure 4. Comparison of migraine characteristics of the groups at the follow-up visits.

Table 6: Comparison of the percentage changes in migraine characteristics of the groups at the follow-up visits compared to the baseline values

Migraine characteristics	Follow-up visits	Median (25–75% percentiles)		P-*value*
		Group GON	Group SPG	
Number of headache days in a month	Baseline vs. 1st month	80.62 (60.0–87.29)	75.0 (0.0– 90.0)	0.366
	Baseline vs. 3rd month	81.25 (4.11–92.64)	85.0 (30.0–90.0)	0.727
Headache frequency in a month	Baseline vs. 1st month	74.17 (31.77–86.67)	70.0 (0.0–90.0)	0.859
	Baseline vs. 3rd month	72.38 (38.96–87.29)	83.33 (11.67–90.0)	0.813
Mean headache attack duration (hours)	Baseline vs. 1st month	66.67 (23.33–82.73)	23.81 (0.0–70.0)	0.011
	Baseline vs. 3rd month	66.67 (23.33–89.93)	37.5 (0.0–75.0)	0.047
Mean pain severity (0–100 mm)	Baseline vs. 1st month	42.22 (20.56–69.18)	20.0 (0.0–55.55)	0.080
	Baseline vs. 3rd month	38.75 (13.33–77.08)	28.57 (0.0–56.35)	0.178

showed a decrease in acute drug use in the short and medium terms with a repeated transnasal SPG blockade in patients with chronic migraine, including the subgroup associated with medication overuse. One of the contributions of our study to the current literature is that chronic migraine with medication overuse can be improved with GON and transnasal SPG blockade. Krebs *et al*.[28] investigated the clinical outcomes following repeated transnasal SPG blockade in patients with chronic migraine accompanied by medication overuse and the functional effect of the blockade on neuroanatomical pathways. They reported an improvement in the number of moderate and severe headache days in a month, as well as a significant improvement in the central executive network connection and in the pain processing centers of the brain.[28]

Our study did not detect any persistent, severe, or disabling adverse effects or complications in either treatment group. The available literature indicates that adverse effects can occur in 2.4-99.6% of cases with GON blockade in patients with chronic migraine. The most common of these adverse effects are local pain in the procedure area, vertigo, and vasovagal syncope.[29] In the present study, local pain developed in the procedure area at a rate of 8.11%, which is consistent with the literature. Conversely, the rate of cases in which severe migraine attacks were triggered by a GON blockade was higher in our study than reported in the literature. Cady *et al*.[25] observed that the most common complications were an unpleasant taste, lacrimation, numbness in the mouth, and nasal discharge in patients who underwent transnasal SPG blockade. Lacrimation occurred in the great majority of our patients who underwent SPG. The incidence of dizziness and nausea/vomiting was similar to previous studies on SPG blockade[17,25], and we did not detect any patients with these complaints. No patient developed any life-threatening or serious adverse effects. Direct group comparison was not possible due to the different adverse effect profiles associated with each procedure.

Our study showed transformation into low-frequency episodic migraine in 67.57% and 63.4% of the chronic migraine patients who underwent GON and SPG blockades, respectively. A neurophysiological study has suggested that conversion to episodic migraine in patients with chronic migraine following a GON blockade treatment occurs due to an increased serotonergic afferent effect.[30] Another contribution of our study to the literature is that transformation to episodic migraine can also be achieved in chronic migraine using transnasal SPG blockade.

The main limitation of our study was its retrospective design. A second limitation was that psychiatric problems were not evaluated with structured psychiatric assessment tools. According to the International Headache Society recommendations, psychiatric conditions should be carefully analyzed in studies involving prophylactic treatment of chronic migraine.[3]

In conclusion, both transnasal SPG blockade and proximal GON blockade are safe alternatives for prophylaxis in patients with chronic migraine. Further elucidation of the clinical efficacy will require randomized, double-blind, placebo-controlled studies that compare blockades with different doses and types of local anesthetics administered at various application intervals.

DISCLOSURE

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Conflict of interest: None.

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