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Altered serum short-chain fatty acid profiles in episodic and chronic migraine and their modulation by preventive treatment

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Abstract

Background Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are gut-microbiota-derived metabolites implicated in gut–brain communication. This study aimed to characterize serum SCFA profiles in individuals with episodic migraine (EM) or chronic migraine (CM) compared with healthy controls (HC) and to examine associations between preventive treatment and these metabolites.

Methods Adults with EM, CM, and age- and sex-matched HC were enrolled. Serum levels of acetate, propionate, and butyrate were quantified using liquid chromatography–tandem mass spectrometry. Group differences in SCFA levels were assessed using Quade's nonparametric analysis of covariance, adjusting for age, sex, and body mass index. Multiple linear regression examined independent associations between preventive treatment and SCFA levels. Moderation analysis evaluated whether preventive treatment modified the association between SCFA levels and headache days per 30 days.

Results Of the 476 participants (HC: $n=108$; EM: $n=190$; CM: $n=178$), those with EM or CM without preventive treatment had lower serum butyrate levels than did HC (EM: $p=0.001$; CM: $p=0.005$), with no significant differences in acetate or propionate. Preventive treatment was independently associated with higher serum propionate levels (B = 0.805, 95% confidence interval [CI] = 0.395–1.215, $p<0.001$) in those with CM but not in those with EM. Although preventive treatment did not significantly modify associations between SCFA levels and headache days per 30 days, higher butyrate levels were associated with a greater number of headache days in participants receiving preventive treatment (B = 7.967, 95% CI = 2.481–13.453, $p=0.005$).

Conclusions Serum SCFA profiles differed according to migraine status and preventive treatment use. Our findings highlight potential interactions among migraine, preventive therapy, and SCFA metabolism, warranting longitudinal studies to clarify directionality and underlying mechanisms.

Keywords Migraine disorders, Short-chain fatty acids, Gut-brain axis, Preventive treatment

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Background

Migraine affects more than one billion people worldwide and imposes a substantial burden on individuals' daily functioning and quality of life [1, 2]. Migraine ranks as the second leading cause of disability worldwide, particularly among individuals of working age, thereby contributing to a significant socioeconomic burden [2, 3]. However, a considerable proportion of individuals with migraine remain undertreated or experience suboptimal outcomes owing to under- or misdiagnosis, limited treatment efficacy, adverse effects, and poor adherence [4, 5]. These challenges underscore the necessity for novel diagnostic biomarkers, and more effective and better-tolerated therapeutic options [6].

The gut–brain axis has emerged as a potential contributor in the pathogenesis of various neurological disorders, including migraine [7, 8]. This bidirectional communication system links the gastrointestinal system and the central nervous system (CNS), allowing reciprocal regulation through neural, hormonal, and immune pathways [9]. The CNS modulates gastrointestinal functions, including motility, secretion, and visceral sensitivity [10]. Conversely, the gut microbiota exerts influence on the brain via several pathways, including vagus nerve activation, modulation of systemic inflammation through cytokines, and generation of neuroactive microbial metabolites [9, 11].

Short-chain fatty acids (SCFAs) have been identified as key mediators of gut–brain communication [12, 13]. SCFAs, which are primarily produced via the anaerobic fermentation of dietary fibers by gut microbiota, are involved in a broad range of physiological processes, including the regulation of immune response, the maintenance of intestinal barrier integrity, the modulation of host energy metabolism, and epigenetic regulation [13]. Importantly, SCFAs are capable of crossing the blood–brain barrier and modulating CNS function by influencing microglial activation, neurotransmitter biosynthesis, and the expression of neurotrophic factors [14–16]. Acetate, propionate, and butyrate—the three principal SCFAs in the human gut—account for approximately 80% of the total SCFA content [17]. Alterations in the levels of these SCFAs have been linked to several neurological diseases, supporting their role as bioactive signaling molecules [18–22].

Gut dysbiosis and alterations in SCFA levels may be implicated in the pathophysiology of migraine [7, 23]. However, there is a paucity of data on serum SCFA levels in individuals with migraine [23, 24]. Moreover, the potential impact of preventive migraine therapy on SCFA profiles has not been systematically examined. Therefore, this study aimed to investigate whether serum levels of acetate, propionate, and butyrate differ among individuals with episodic migraine (EM), chronic migraine (CM), and healthy controls (HC). We further examined whether preventive treatment is associated with changes in circulating SCFA levels, thereby exploring the potential links between therapeutic intervention and gut–brain axis–related metabolic profiles.

Methods

Standard protocol approvals, registrations, and patient consents

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University (IRB No. 2019-1403-005), and was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Prior to inclusion in the study, written informed consent was obtained from all the participants.

Participants

Participants were recruited from the neurology outpatient clinic at a tertiary hospital in the Republic of Korea between October 2019 and December 2022. Inclusion criteria were (a) adults aged 19–65 years, and (b) diagnosis of EM or CM according to the International Classification of Headache Disorders, third edition (ICHD-3) [25]. EM was defined as migraine without aura (code 1.1) or migraine with aura (code 1.2) occurring on < 15 days per month for at least 3 months. CM (code 1.3) was defined as headache occurring on at least 15 days per month for > 3 months, with at least 8 days meeting the criteria for migraine with or without aura. For the purpose of this study, migraine subtypes were classified solely as EM or CM based on these definitions.

Exclusion criteria were (a) current or past treatment for gastrointestinal, medical, psychiatric, or neurological disorders other than anxiety, depression, medication-overuse headache (code 8.2), or fibromyalgia; (b) significant dietary habit changes within 6 months before enrollment; (c) use of prebiotics or probiotics within 1 year before enrollment; and (d) pregnancy or lactation. Participants taking preventive medications for migraine were eligible only if their dosage had been stable for at least 3 months and they fully understood the study protocol. Those receiving antidepressants for migraine prevention were included, whereas individuals taking antidepressants for depression were excluded. Patients receiving calcitonin gene-related peptide (CGRP)-targeted preventive therapies, including anti-CGRP monoclonal antibodies and gepants, were excluded. The diagnoses of EM and CM and the assessment of clinical characteristics and comorbidities were conducted by a headache specialist (MKC) through structured interviews using established diagnostic criteria.

To characterize preventive treatment status, we reviewed individual medical records to identify the specific preventive medications in use (anticonvulsants,

beta-blockers, antidepressants, and calcium channel blockers), together with their daily dosages and the duration for which the current regimen had been maintained without change. Adherence was confirmed through chart review and clinician interview. Detailed information is provided in Supplementary Table 1.

Control participants were recruited through advertisements and selected based on their age, sex, and body mass index (BMI) to match the profiles of participants in the EM and CM groups. To qualify as HC, individuals were required to meet both of the following criteria: (a) no headaches in the past year, and (b) no lifetime history of migraine or probable migraine episodes. Additionally, exclusion criteria were applied to the control group.

Sample size

To our knowledge, studies investigating SCFA levels in individuals with migraine are currently lacking. Consequently, the requisite sample size was estimated on the basis of a preceding study that had measured serum SCFA concentrations in patients with irritable bowel syndrome, a prevalent comorbidity of migraine [26, 27]. Assuming an equal allocation of participants between the disease and control groups, the minimum sample sizes required to detect significant differences in acetate, propionate, and butyrate levels with 80% power at a 5% significance level were calculated to be 10, 24, and 51, respectively. Accordingly, the enrollment target was set at a minimum of 100 participants in each of the EM, CM, and HC groups to ensure sufficient statistical power to examine the relationship between SCFA levels and clinical characteristics.

Assessment of anxiety, depression, medication overuse, and fibromyalgia

The assessments for anxiety and depression were conducted using the Generalized Anxiety Disorder-7 (GAD-7) scale and the Patient Health Questionnaire-9 (PHQ-9), respectively [28, 29]. Scores of 8 or higher on the GAD-7 indicated the presence of anxiety, while scores of 10 or higher on the PHQ-9 indicated depression. Medication overuse was defined as acute medication use exceeding the ICHD-3 overuse threshold for at least 3 months. Specifically, it was defined as the use of simple analgesics or non-steroidal anti-inflammatory drugs on 15 days or more per month, or the use of triptans, ergot derivatives, opioids or combination analgesics on 10 days or more per month [25]. The diagnostic criteria for medication-overuse headache, which additionally require headache on 15 days or more per month, were not applied in this study. The diagnosis of fibromyalgia was made in accordance with the criteria established by the American College of Rheumatology in 2016 [30].

Serum preparation

For participants with EM, blood sampling was performed only after at least 48 h had passed since the resolution of a typical migraine attack, during a headache-free period. The absence of prodromal symptoms was confirmed via structured interviews by MKC at the time of sampling. For participants with CM, blood samples were obtained during periods of mild or less headache intensity. A 5 mL sample of blood was drawn from the antecubital vein into a vacutainer SSTTM tube (Becton Dickinson, Franklin Lakes, NJ, USA) between 9:00 and 12:00 a.m. The whole blood sample was allowed to coagulate at 22–25 °C for 15 min. Subsequently, the sample was subjected to centrifugation at 1,500 g for 15 min at a temperature of 4 °C to facilitate the separation of the clot from the serum. The serum (supernatant) obtained post-centrifugation was carefully transferred to a storage container and frozen at – 70 °C for future analysis.

Measurement of SCFAs

Serum levels of acetate, propionate, and butyrate were determined using liquid chromatography–tandem mass spectrometry (LC–MS/MS), as described in our earlier study [24].

Supplementary Method 1 provides the sources of all chemicals and reagents. Stock solutions of acetic acid (100 mM), propionic acid (10 mM), and butyric acid (10 mM) were prepared in deionized water and diluted in 2% albumin to obtain calibration standards. Calibration standards were prepared at concentrations of 5, 10, 25, 50, 100, and 250 μM for acetic acid, and 0.2, 0.5, 1, 2.5, 5, 10, and 25 μM for both propionic and butyric acids. Stock solutions of stable isotope-labeled SCFAs including [D4]-acetic acid (100 μM), [D5]-propionic acid (10 μM), and [D7]-butyric acid (10 μM), were used as internal standards.

For each serum sample and calibration standard, 10 μL of the internal standard mixture was added to 10 μL of sample. Derivatization was performed as follows. Briefly, 100 μL of 15 mM 3-nitrophenylhydrazine hydrochloride and 2 mM N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride in methanol containing 2% pyridine was added to the mixture and incubated at 25 °C for 30 min. After centrifugation at 16,000 g for 5 min (repeated three times), 20 μL of the supernatant was obtained, quenched with 200 μL of 0.1% formic acid, and 10 μL of the resulting solution was injected into the LC–MS/MS system.

Chromatographic separation was performed using an Agilent 1290 Infinity II LC system (Agilent Technologies, Santa Clara, CA, USA) equipped with an ACQUITY UPLC BEH C18 column (2.1 × 100 mm, 1.7 μm, 130 Å; Waters, Milford, MA, USA). Mass spectrometry was conducted using a QTRAP 5500 triple-quadrupole

mass spectrometer (AB SCIEX, Foster City, CA, USA) equipped with electrospray ionization in negative ion mode and operated in multiple reaction monitoring mode for quantification (Supplementary Table 2). Calibration curves were generated from peak area ratios of analytes to internal standards across defined concentration ranges. Data acquisition and analysis were performed using Analyst 1.6.3 software (AB SCIEX). Intra-assay ($n = 3$) and inter-assay ($n = 5$) precision for acetic, propionic, and butyric acids were assessed using quality control samples at three concentration levels. All coefficients of variation were within acceptable limits (Supplementary Table 3).

Statistical analysis

Categorical variables are presented as counts with percentages and compared using the chi-squared test or Fisher's exact test, as appropriate. Non-normally distributed continuous variables are presented as medians with interquartile ranges and compared using the Mann–Whitney U test or Kruskal–Wallis test. Unless otherwise specified, tests were two-sided with p-value < 0.05.

As serum SCFA levels did not follow a normal distribution, three-group comparisons of SCFAs were performed using Quade's nonparametric analysis of covariance (ANCOVA), with age, sex, and BMI as covariates in each of the following settings: (1) HC, EM, and CM; (2) HC, EM without preventive treatment (EMw/oP), and CM without preventive treatment (CMw/oP); (3) HC, EM with preventive treatment (EMwP), and CM with preventive treatment (CMwP); and (4) HC, migraine with preventive treatment, and migraine without preventive treatment. For multiple comparisons among the groups, the Bonferroni correction was applied (significance threshold adjusted to $p < 0.017$). As a sensitivity analysis, these three-group comparisons were repeated using linear models with log-transformed SCFA concentrations as dependent variables, adjusting for age, sex, and BMI. The full results of the sensitivity analyses are provided in the Supplementary Materials.

Among participants receiving preventive treatment, serum SCFA levels were compared between users and non-users of each preventive medication class. Participants were classified as users of a given class if that class was included in their regimen, regardless of concomitant use of other preventive medications. This definition was chosen to reflect real-world prescribing patterns and to maintain adequate sample size for statistical comparison. Group differences were evaluated using Quade's nonparametric ANCOVA adjusted for age, sex, and BMI.

To examine differences by predefined characteristics, serum SCFA levels were compared between participants with versus without each demographic or clinical characteristic, or migraine-related comorbidity, using the Mann–Whitney U test. These exploratory contrasts were conducted in three datasets: (1) the pooled migraine cohort (EM and CM groups); (2) migraine without preventive treatment (Mw/oP); and (3) migraine with preventive treatment (MwP). Within each dataset, the Benjamini–Hochberg procedure was used to control the false discovery rate (FDR).

In the pooled migraine cohort comprising EM and CM, exploratory comparisons indicated that serum propionate—but not acetate or butyrate—varied by preventive treatment status. To examine the independent association between preventive treatment and serum propionate levels, we constructed a multiple linear regression model adjusting for demographic variables (age, sex, and BMI), headache characteristics that significantly differed between EM and CM in the univariable analyses, and migraine-related comorbidities including depression, anxiety, and fibromyalgia. To further examine whether this association differed by migraine subtype (EM or CM), we conducted a linear regression analysis that included an interaction term between preventive treatment and migraine subtype, adjusting for age, sex, and BMI.

To examine whether preventive treatment modified the association between SCFA levels and migraine clinical characteristics, we conducted a moderation analysis using the number of headache days per 30 days as the dependent variable. For each SCFA, linear models included the SCFA level, preventive treatment status, and their interaction, with age, sex, and BMI as covariates. All continuous variables were mean-centered prior to analysis to reduce multicollinearity. Moderation analysis was implemented using the PROCESS macro (version 4.2) in IBM SPSS Statistics software (version 27.0). For all linear models, residual diagnostics were examined, and multicollinearity was assessed using variance inflation factors.

All statistical analyses were performed using IBM SPSS Statistics v27.0 and R v4.4.1, and all figures were created in R using the ggplot2 and patchwork packages.

Results

Demographic and clinical characteristics of HC, EM, and CM

A total of 476 participants were enrolled, with 108, 190, and 178 participants in the HC, EM, and CM groups, respectively. Table 1 presents the demographic and clinical characteristics. Sex, age, and BMI did not differ significantly among the groups. Participants with CM had a significantly higher median number of headache days per 30 days compared to those with EM (20.0 vs. 4.0, $p < 0.001$). Beyond headache frequency, CM was characterized by lower frequencies of unilateral pain and migraine with aura, but higher prevalence of phonophobia. CM was also associated with a greater clinical

Table 1 Demographic and clinical characteristics of participants

	EM (*n* = 190)	CM (*n* = 178)	HC (*n* = 108)	*p*-value
Demographics				
Age, years	40.0 (31.0–49.0)	43.0 (33.0–52.0)	42.5 (33.0–54.0)	0.168
Sex, female, *n* (%)	159 (83.7)	162 (91.0)	98 (90.7)	0.059
BMI, kg/m^2	21.9 (19.9–24.3)	22.5 (20.0–24.8)	22.6 (20.3–24.8)	0.453
Headache Characteristics				
Headache days per 30 days	4.0 (3.0–7.3)	20.0 (16.0–30.0)		< 0.001*
Severe pain intensity, *n* (%)	159 (83.7)	156 (87.6)		0.280
Unilateral location, *n* (%)	112 (58.9)	73 (41.0)		< 0.001*
Pulsating quality, *n* (%)	181 (95.3)	174 (97.8)		0.196
Aggravation by routine physical activity, *n* (%)	148 (77.9)	149 (83.7)		0.158
Nausea, *n* (%)	175 (92.1)	166 (93.3)		0.672
Vomiting, *n* (%)	85 (44.7)	74 (41.6)		0.540
Photophobia, *n* (%)	88 (46.3)	97 (54.5)		0.117
Phonophobia, *n* (%)	97 (51.1)	118 (66.3)		0.003*
Migraine with aura, *n* (%)	18 (9.5)	5 (2.8)		0.008*
Medication overuse, *n* (%)	4 (2.1)	24 (13.5)		< 0.001*
Preventive treatment, *n* (%)	29 (15.3)	44 (24.7)		0.023*
Migraine Comorbidities				
Anxiety, *n* (%)	36 (18.9)	59 (33.1)		0.002*
Depression, *n* (%)	35 (18.4)	80 (44.9)		< 0.001*
Fibromyalgia, *n* (%)	22 (11.6)	89 (50.0)		< 0.001*

For age, sex, BMI, and serum SCFA levels, CM, EM and HC groups are compared. For other clinical variables, CM and EM groups are compared

Quade's nonparametric ANCOVA was performed to compare serum SCFA levels across groups, adjusting for age, sex, and BMI

* $p < 0{\cdot}05$

[a] Significant difference between EM and HC groups in a post hoc analysis

[b] Significant difference between CM and HC groups in a post hoc analysis

Abbreviations: BMI = body mass index; CM = chronic migraine; EM = episodic migraine; HC = healthy control; SCFA = short-chain fatty acids

burden, including higher rates of medication overuse, preventive treatment use, and migraine-related comorbidities such as anxiety, depression, and fibromyalgia.

Among the 73 participants with EM or CM who were receiving preventive treatment, 46 (63.0%) were on a single medication, while 27 (37.0%) were using two or more. Anticonvulsants were the most frequently used class of medication (86.3%), with topiramate predominating among them (69.9%). Beta-blockers and antidepressants were used by 31.5% and 16.4% of participants, respectively. The calcium channel blocker, flunarizine, was used by 6.8% of participants. No significant differences were observed between the EM and CM groups regarding the type or number of preventive medications used (Supplementary Table 4).

Serum SCFA levels in HC, EM, and CM

Serum acetate and propionate levels did not differ significantly among the groups (acetate: 53.5 μM [36.1–99.4] in HC, 56.0 [34.0–104.5] in EM, and 60.2 [36.8–97.4] in CM, $p = 0.738$; propionate: 1.2 μM [0.6–1.9] in HC, 1.3 [0.7–1.9] in EM, and 1.4 [0.6–2.3] in CM, $p = 0.273$). In contrast, serum butyrate levels were significantly lower in the EM group (0.4 μM [0.3–0.6]) compared with HC (0.5 [0.4–0.8], $p < 0.001$). A reduction in butyrate levels was also observed in the CM group (0.4 [0.3–0.6], $p = 0.020$) relative to HC; however, this difference was not significant after multiple-comparison correction. No significant difference was observed in butyrate levels between the EM and CM groups ($p = 0.119$) (Fig. 1).

We further analyzed serum levels of acetate, propionate and butyrate based on the presence or absence of specific demographic or clinical characteristics, or migraine-related comorbidities among participants with migraine (pooled EM and CM groups) (Supplementary Table 5). Only a significant difference was observed for propionate, with higher levels found in participants receiving preventive treatment than in those not receiving the treatment (1.6 μM [1.3–2.4] vs. 1.3 [0.6–1.9] respectively, FDR-adjusted $p < 0.001$).

Serum SCFA levels in HC, EM without preventive treatment, and CM without preventive treatment

Demographic and clinical characteristics of the HC, EMw/oP, and CMw/oP groups are summarized in Supplementary Table 6. Serum acetate and propionate levels were comparable across the three groups (acetate: 53.5 μM [36.1–99.4] in HC, 56.6 [33.9–118.2] in EMw/oP,

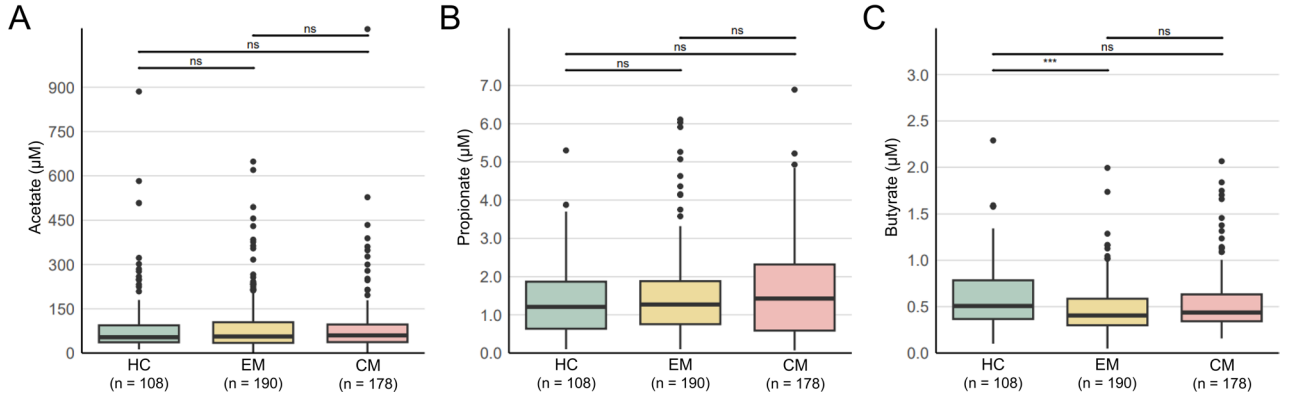

Fig. 1 Serum (**A**) acetate, (**B**) propionate, and (**C**) butyrate levels in healthy controls, participants with episodic migraine and chronic migraine Boxplots represent the interquartile range with median values, and outliers are plotted as points. Between-group differences were tested using Quade's nonparametric analysis of covariance, adjusted for age, sex, and body mass index. Significance levels are indicated as $p < 0.001$ (***), and ns (not significant). Abbreviations: CM = chronic migraine; EM = episodic migraine; HC = healthy control

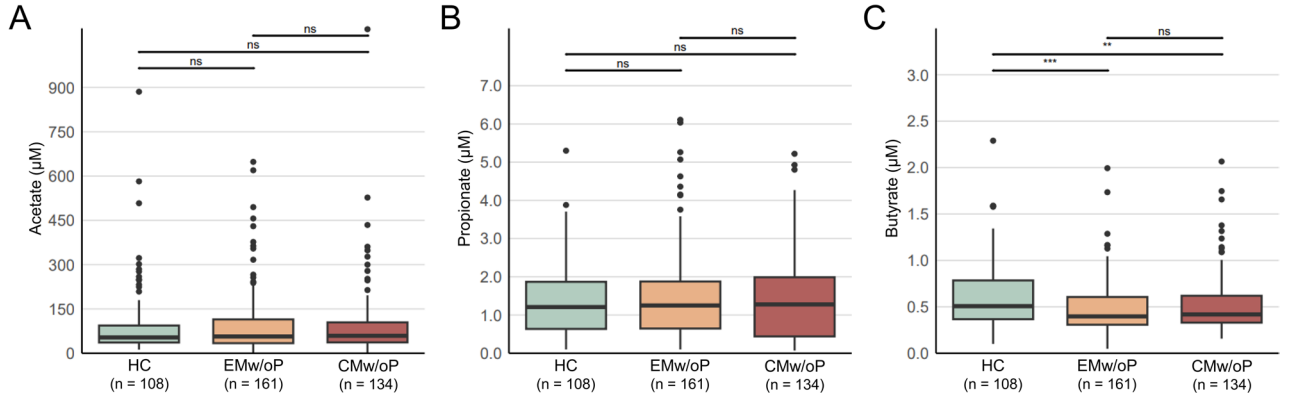

Fig. 2 Serum (**A**) acetate, (**B**) propionate, and (**C**) butyrate levels in healthy controls, participants with episodic migraine without preventive treatment and chronic migraine without preventive treatment. Boxplots represent the interquartile range with median values, and outliers are plotted as points. Between-group differences were tested using Quade's nonparametric analysis of covariance, adjusted for age, sex, and body mass index. Significance levels are indicated as $p < 0.01$ (**), $p < 0.001$ (***), and ns (not significant). Abbreviations: CMw/oP = chronic migraine without preventive treatment; EMw/oP = episodic migraine without preventive treatment; HC = healthy control

and 59.3 [36.6–105.9] in CMw/oP, $p = 0.273$; propionate: 1.2 μM [0.6–1.9] in HC, 1.3 [0.6–1.9] in EMw/oP, and 1.3 [0.4–2.0] in CMw/oP, $p = 0.837$). Notably, compared with HC (0.5 μM [0.4–0.8]), serum butyrate levels were significantly reduced in both EMw/oP (0.4 [0.3–0.6], $p = 0.001$) and CMw/oP groups (0.4 [0.3–0.6], $p = 0.005$). No significant difference was observed in butyrate levels between the EMw/oP and CMw/oP groups ($p = 0.592$) (Fig. 2).

Among participants with EM or CM who were not receiving preventive treatment, no significant differences in SCFAs were observed across with versus without subgroups defined by demographic or clinical characteristics, or migraine-related comorbidities (all FDR-adjusted $p > 0.05$) (Supplementary Table 7).

Serum SCFA levels in HC, EM with preventive treatment, and CM with preventive treatment

Demographic and clinical variables for the HC, EMwP, and CMwP groups are shown in Supplementary Table 8. Serum acetate and butyrate levels did not differ among the three groups (acetate: 53.5 μM [36.1–99.4] in HC, 49.1 [36.0–83.3] in EMwP, and 61.3 [37.2–92.6] in CMwP, $p = 0.739$; butyrate: 0.5 μM [0.4–0.8] in HC, 0.4 [0.3–0.5] in EMwP, and 0.5 [0.4–0.7] in CMwP, $p = 0.067$). However, serum propionate levels were significantly higher in the CMwP group (2.0 μM [1.5–2.7]) than in the EMwP (1.4 [1.0–2.2], $p = 0.012$) and HC groups (1.2 [0.6–1.9], $p < 0.001$). No significant difference was observed in propionate levels between the EMwP and HC groups ($p = 0.198$) (Fig. 3).

Among participants with EM or CM receiving preventive treatment, no significant differences in SCFAs were observed across with versus without subgroups defined by demographic or clinical characteristics, or migraine-related comorbidities (Supplementary Table 9).

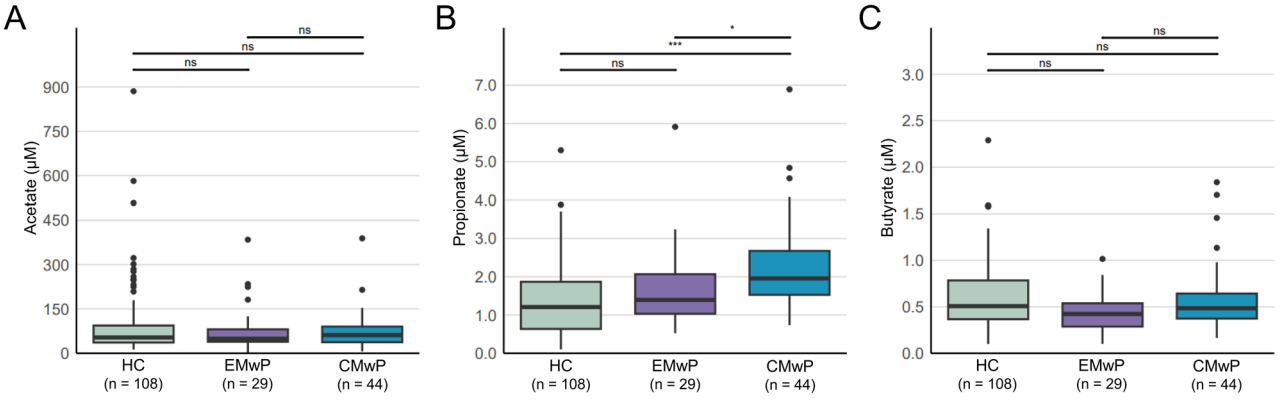

Fig. 3 Serum (**A**) acetate, (**B**) propionate, and (**C**) butyrate levels in healthy controls, participants with episodic migraine with preventive treatment and chronic migraine with preventive treatment. Boxplots represent the interquartile range with median values, and outliers are plotted as points. Between-group differences were tested using Quade's nonparametric analysis of covariance, adjusted for age, sex, and body mass index. Significance levels are indicated as $p < 0.017$ (*), $p < 0.001$ (***), and ns (not significant). Abbreviations: CMwP = chronic migraine with preventive treatment; EMwP = episodic migraine with preventive treatment; HC = healthy control

Serum SCFA levels according to preventive treatment status and medication class

We further compared serum SCFA levels across HC, MwP, and Mw/oP, to directly contrast treatment status and to distinguish disease-related from treatment-related alterations. Serum acetate levels did not differ significantly among the groups (53.5 μM [36.1–99.4] in HC, 58.5 [37.2–87.4] in MwP, 57.8 [35.0–109.3] in Mw/oP, $p = 0.740$). In contrast, serum propionate levels were significantly higher in MwP (1.6 μM [1.3–2.4]) than in HC (1.2 [0.6–1.9], $p < 0.001$) and Mw/oP (1.3 [0.6–1.9], $p < 0.001$), whereas no difference was observed between Mw/oP and HC ($p = 0.887$). For butyrate, Mw/oP (0.4 μM [0.3–0.6]) exhibited significantly lower levels compared with HC (0.5 [0.4–0.8], $p < 0.001$), while no significant differences were found between HC and MwP (0.5 [0.3–0.6], $p = 0.118$) or between MwP and Mw/oP ($p = 0.208$) (Supplementary Fig. 1).

To assess class-specific associations, serum propionate and butyrate levels were compared between users and non-users of each preventive medication class. After excluding calcium channel blockers owing to the small number of users, no significant differences in serum propionate or butyrate levels were found between users and non-users of anticonvulsants, β-blockers, or antidepressants. Among participants receiving migraine preventive medications, 69.9% were prescribed topiramate, and serum propionate and butyrate levels did not differ significantly between users and non-users of topiramate (Supplementary Tables 4 and 10).

Associations between preventive treatment and serum propionate levels in participants with migraine

As only serum propionate differed by preventive treatment status in the pooled migraine cohort comprising EM and CM ($n = 368$), we examined whether preventive treatment was independently associated with serum propionate after adjusting for demographics, headache characteristics, and comorbidities. Multiple linear regression analysis revealed that preventive treatment was independently associated with higher serum propionate levels (B = 0.556, 95% confidence interval [CI]: 0.248 to 0.863, $p < 0.001$) (Table 2). None of the other covariates including age, sex, BMI, number of headache days per 30 days, unilateral pain, phonophobia, aura, medication overuse, anxiety, depression, or fibromyalgia were significantly associated with serum propionate levels.

Table 2 Multiple regression models examining the association between serum propionate levels and preventive treatment

Variables	B (95% CI)	*p*-value
Preventive treatment	0.556 (0.248, 0.863)	< 0.001[a]
Age, years	–0.009 (–0.019, 0.002)	0.108
Sex, female	–0.010 (–0.394, 0.374)	0.958
BMI, kg/m^2	0.015 (–0.020, 0.051)	0.398
Number of headache days per 30 days	0.002 (–0.012, 0.015)	0.823
Unilateral location	–0.050 (–0.305, 0.205)	0.700
Phonophobia	–0.199 (–0.447, 0.048)	0.114
Migraine with aura	–0.181 (–0.689, 0.328)	0.486
Medication overuse	0.030 (–0.443, 0.502)	0.902
Anxiety	–0.036 (–0.385, 0.314)	0.841
Depression	0.006 (–0.339, 0.350)	0.974
Fibromyalgia	0.223 (–0.074, 0.520)	0.140

[a] $p < 0.05$

Abbreviations: BMI = body mass index; CI = confidence interval

To assess heterogeneity of this association between EM and CM, an interaction term between preventive treatment and migraine subtype was included in the regression model. Although the interaction term did not reach statistical significance (B = 0.596, 95% CI: – 0.011 to 1.203, $p = 0.054$), subgroup analyses showed that preventive treatment was significantly associated with

Table 3 Moderation analysis of the association between serum propionate levels and number of headache days per 30 days by preventive treatment

Variable	B	SE	t	*p*-value	95% CI	
					Lower	Upper
Serum propionate						
Without preventive treatment	0.074	0.507	0.146	0.884	−0.923	1.071
With preventive treatment	1.624	1.249	1.300	0.194	−0.833	4.082
Preventive treatment	3.315	1.518	2.184	0.030[a]	0.330	6.300
Serum propionate x Preventive treatment	1.550	1.348	1.150	0.251	−1.101	4.202
Age	0.078	0.047	1.652	0.099	−0.015	0.171
Sex	3.916	1.638	2.391	0.017[a]	0.695	7.137
BMI	0.299	0.163	1.841	0.066	−0.020	0.619

Model $R^2 = 0.066$, $F(6, 361) = 3.241$, $p = 0.004$

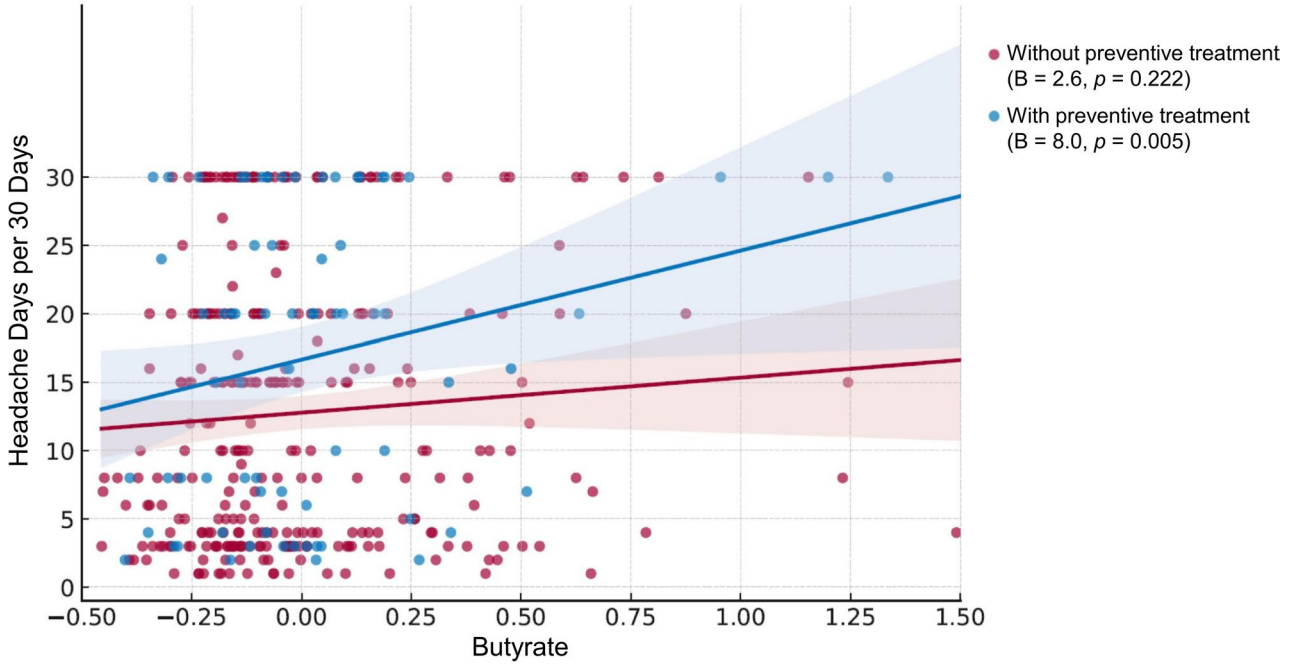

Fig. 4 Interaction between serum butyrate and preventive medication use on headache days per 30 days. Butyrate values were mean-centered for analysis and visualization. Predicted headache days per 30 days across centered butyrate levels are plotted separately according to preventive medication use. Shaded areas represent 95% confidence intervals. Analyses were adjusted for age, sex, and body mass index

higher propionate levels in the CM group (B = 0.805, 95% CI: 0.395 to 1.215, $p < 0.001$), but not in the EM group (B = 0.217, 95% CI: −0.236 to 0.669, $p = 0.346$) (Supplementary Table 11).

Moderation analysis of the association between serum SCFA levels and headache days according to preventive treatment status

We evaluated whether preventive treatment moderated the association between SCFA levels and the number of headache days per 30 days. Serum propionate showed no evidence of moderation by preventive treatment (B = 1.550, 95% CI: −1.101 to 4.202, $p = 0.251$). The association between serum propionate levels and headache days was also non-significant in participants receiving and not receiving preventive treatment (Table 3).

For butyrate, the interaction term with preventive treatment was not significant (B = 5.398, 95% CI: −1.499 to 12.295, $p = 0.125$). However, in stratified analyses, serum butyrate levels were significantly associated with a greater number of headache days among participants receiving preventive treatment (B = 7.967, 95% CI: 2.481 to 13.453, $p = 0.005$), but not among those not receiving treatment (B = 2.569, 95% CI: −1.563 to 6.701, $p = 0.222$), as shown in Fig. 4 and detailed in Table 4.

As a sensitivity analysis, all three-group comparisons were repeated using covariate-adjusted linear models with log-transformed SCFA values. These analyses showed similar overall patterns of group differences,

Table 4 Moderation analysis of the association between serum butyrate levels and number of headache days per 30 days by preventive treatment

Variable	B	SE	t	*p*-value	95% CI	
					Lower	Upper
Serum butyrate						
Without preventive treatment	2.569	2.101	1.223	0.222	−1.563	6.701
With preventive treatment	7.967	2.790	2.856	0.005[a]	2.481	13.453
Preventive treatment	3.880	1.393	2.785	0.006[a]	1.140	6.619
Serum butyrate x Preventive treatment	5.398	3.507	1.539	0.125	−1.499	12.295
Age	0.071	0.048	1.472	0.142	−0.024	0.166
Sex	3.661	1.641	2.231	0.026[a]	0.433	6.888
BMI	0.307	0.162	1.892	0.059	−0.012	0.627

Model $R^2 = 0.076$, $F(6, 361) = 5.787$, $p < 0.001$

although statistical significance differed for some comparisons (Supplementary Tables 12–15).

Discussion

We investigated serum SCFAs in participants with EM and CM and examined the potential influence of preventive treatment. Three main findings were observed: (1) Compared with HC, serum butyrate levels were lower in participants with both EM and CM who were not receiving preventive treatment, whereas acetate and propionate levels did not differ significantly; (2) Preventive treatment was associated with higher serum propionate levels in participants with CM but not in those with EM; and (3) Among participants receiving preventive treatment, higher serum butyrate levels were associated with a greater number of headache days per 30 days, whereas no such association was observed in those without preventive treatment. These findings suggest distinct SCFA patterns related to migraine phenotype and preventive treatment status.

Among participants not receiving preventive treatment, serum butyrate levels were lower in both EM and CM than in HC. This pattern aligns with prior microbiome research and suggests that reduced butyrate may represent a metabolic feature associated with migraine. Butyrate is produced primarily by gut bacteria such as *Faecalibacterium prausnitzii* and *Eubacterium rectale/Roseburia spp* [31, 32]. It contributes to intestinal barrier integrity by serving as an energy source for colonic epithelial cells and regulates anti-inflammatory signaling and neurotransmitter pathways through mechanisms including histone deacetylase inhibition [33]. Prior studies have reported reduced abundance of butyrate-producing bacteria in migraine [23, 34, 35]. These include a systematic review highlighting lower relative abundance of *Faecalibacterium* [23], as well as a study showing that *Roseburia* and *Agathobacter* are less abundant in both EM and CM compared with HC [35], all of which are recognized butyrate producers. Preclinical data further demonstrate that administration of exogenous butyrate can alleviate migraine-like behaviors and modulate both central and enteric inflammatory responses [36, 37]. While our cross-sectional design precludes causal inference, the alignment between our findings and prior studies suggests a plausible association between butyrate and migraine.

In contrast, serum butyrate levels in participants with EM and CM receiving preventive treatment did not differ significantly from those of HC. This finding may reflect partial normalization through treatment-related effects on the gut microbiome. Preclinical data suggest that certain preventive agents, such as topiramate, can increase butyrate-producing bacteria and cecal butyrate concentrations [38]. In our cohort, however, serum butyrate levels did not differ between topiramate users and non-users, indicating that additional factors beyond medication type may be involved.

Preventive treatment was also associated with higher serum propionate levels, but this effect was limited to participants with CM. CM differs from EM in several clinical features, including greater headache burden, higher rates of psychiatric and pain-related comorbidities, and more frequent exposure to preventive medications [39, 40], any of which may influence propionate elevation.

The distinct patterns of butyrate and propionate observed with preventive treatment may partly reflect their differing metabolic fates. Butyrate is extensively consumed by colonocytes and undergoes local oxidation, which limits its appearance in systemic circulation [41]. Propionate, in contrast, is more readily absorbed into the portal vein and can be detected more consistently in serum [41]. As a result, treatment-related changes in microbial fermentation or host metabolism may be more apparent in circulating propionate than in butyrate, even when both are affected.

The influence of preventive treatment on SCFA levels may involve multiple, interacting physiological, metabolic, and behavioral factors. Prior work in patients with CM and medication overuse headache has described gut

dysbiosis skewed toward an inflammatory state, with altered gut microbiota showing associations with systemic inflammatory markers [42]. By reducing migraine burden and associated neuroinflammation, preventive treatment may shift host–microbial interactions, thereby influencing SCFA metabolism. Both butyrate and propionate are involved in immune regulation and gut–brain communication, and reductions in inflammatory activity could affect their production, absorption, or utilization. The more severe and chronic neuroinflammatory state characteristic of CM may also render propionate metabolism more sensitive to these treatment-related physiological shifts, although this remains speculative and warrants further investigation. In addition, preventive agents, such as topiramate and beta-blockers, have been shown to influence systemic metabolic parameters including acid–base balance, resting energy expenditure, and body weight regulation [43–45]. Such medication-related metabolic effects may modulate SCFA metabolism by altering nutrient flux, substrate utilization, or endocrine signaling.

Importantly, pre-existing differences in lifestyle factors, particularly dietary habits, between participants receiving and not receiving preventive treatment may have contributed to the observed SCFA variability [46–48]. Factors such as habitual diet, physical activity, sleep, and health-seeking behaviors, all of which were not systematically assessed in this study, are known to influence SCFA metabolism [49–52]. Given these overlapping biological, pharmacological, and behavioral influences, our cross-sectional design does not permit the isolation of any single explanatory pathway. Further studies are needed to clarify whether the observed shifts in butyrate and propionate reflect treatment-induced changes with clinical relevance. Longitudinal designs that integrate serial SCFA profiling with microbiome and lifestyle data will be critical to disentangle the pathways through which preventive therapies shape host–microbial metabolism in migraine.

A positive association between serum butyrate levels and the number of headache days per month was observed exclusively among participants receiving preventive treatment. At first glance, this finding may seem paradoxical, given the broadly recognized neuroimmunemodulatory and gut barrier-enhancing effects of butyrate [13, 33]. Several potentially overlapping mechanisms may explain this pattern. First, higher migraine burden may trigger a compensatory upregulation of microbial butyrate production, reflecting an adaptive host–microbial response intended to counter persistent neuroinflammation or intestinal barrier dysfunction. Second, individuals receiving preventive treatment may represent a subgroup with more severe or long-standing disease, or with specific lifestyle factors, in whom such compensatory metabolic shifts are more likely to manifest. Third, preventive agents themselves may create a metabolic milieu, through direct host effects or indirect microbial modulation, that facilitates increased butyrate production under conditions of greater disease activity. Given the cross-sectional nature of the data, these interpretations should be considered hypotheses rather than causal inferences. Together, these observations highlight the complex interplay between migraine burden, pharmacologic intervention, and host–microbial metabolic adaptation.

This study has several methodological limitations. One important limitation is that dietary habits and other lifestyle factors that influence SCFA production, such as fiber intake, physical activity, and sleep, were not systematically assessed [49–52]. Although participants with recent dietary changes or probiotic use were excluded to minimize short-term variability, unmeasured differences in habitual diet or lifestyle may have introduced residual confounding. While the relatively homogeneous dietary background of a single-country Korean cohort may have reduced within-group variability, the absence of detailed dietary data limits mechanistic interpretation and generalizability to populations with different ethnic and dietary backgrounds. Another limitation is the absence of gut microbiome profiling, which precluded taxonomic or functional characterization of microbial contributors to SCFA variability. Prior studies have reported migraine-associated gut dysbiosis [23, 34, 35, 42] and have suggested that certain gut microbial taxa may be causally associated with migraine susceptibility [53]. Migraine-associated differences in gut microbiota may be reflected in downstream microbial metabolites, including SCFAs. However, because gut microbiota and SCFAs have not been assessed concurrently in prior studies or in the present study, these associations cannot be interpreted mechanistically. Accordingly, future studies integrating metagenomic and metabolomic approaches will be essential to disentangle microbial, host, and pharmacologic influences on SCFA metabolism.

In addition, the distribution of preventive medications was highly unbalanced, with anticonvulsants, particularly topiramate, prescribed to most participants receiving preventive treatment. As a result, the small numbers in other medication classes limited our ability to identify class-specific differences, and the possibility remains that true class-specific effects exist but were not detected in this study. We also note that reliable information on disease duration was not consistently available, as the timing of migraine onset is often reported retrospectively and can be difficult to define with precision. Accordingly, this variable could not be incorporated into the analyses.

This study also has interpretative limitations. Our analysis was limited to acetate, propionate, and butyrate, which together account for the majority of total SCFA content [17]. Nonetheless, omission of minor

SCFAs narrows the metabolic scope and may have overlooked additional pathophysiologically relevant alterations. Finally, the cross-sectional design precludes causal inference. Although associations between SCFA levels, migraine subtypes, and preventive treatment status were observed, these relationships cannot establish temporal sequence or mechanistic directionality. Prospective studies incorporating longitudinal sampling, serial SCFA measurements, and integrated microbiome assessments will be necessary to elucidate these interactions, clarify temporal pathways, evaluate treatment-related changes, and determine whether alterations in SCFAs represent causes or consequences of migraine and its management.

Despite these limitations, the study offers several notable strengths. First, it represents one of the largest investigations to quantify all three major serum SCFAs in well-characterized cohorts of EM, CM, and healthy controls, each with over 100 participants. The large sample size and detailed clinical phenotyping enabled subgroup analyses by migraine subtype and preventive treatment status. Second, SCFA measurements were performed using consistent and validated procedures, enhancing the reliability of the biochemical data. Third, this is the first study to identify distinct shifts in SCFA profiles associated with preventive treatment, encompassing both compositional patterns and clinical correlations. Finally, our analysis highlights circulating SCFAs as integrative metabolic markers that reflect both microbial activity and host physiology. While causal relationships cannot be inferred, these findings may inform future hypotheses regarding host–microbial interactions in migraine. In light of emerging evidence implicating gut barrier dysfunction and systemic inflammation in migraine chronification [54], the SCFA patterns observed here may hold relevance for gut–brain axis mechanisms in disease progression.

Conclusions

In conclusion, serum SCFA profiling revealed distinct alterations in migraine based on clinical subtype and preventive treatment status. Lower butyrate levels observed in EM participants not receiving preventive treatment may reflect early disease-related changes. In contrast, propionate levels were elevated in CM participants receiving preventive treatment, and butyrate levels showed a positive association with headache frequency in this group. These findings may reflect treatment-associated shifts in SCFA profiles, although causality cannot be inferred. Accordingly, prospective, mechanistic studies are needed to clarify causal relationships and the physiological relevance of SCFA changes in migraine.

Abbreviations

ANCOVA	Analysis of covariance
BMI	Body mass index
CGRP	Calcitonin gene-related peptide
CM	Chronic migraine
CMwP	Chronic migraine with preventive treatment
CMw/oP	Chronic migraine without preventive treatment
CNS	Central nervous system
EM	Episodic migraine
EMwP	Episodic migraine with preventive treatment
EMw/oP	Episodic migraine without preventive treatment
FDR	False discovery rate
GAD-7	Generalized Anxiety Disorder-7
HC	Healthy control
ICHD-3	International Classification of Headache Disorders, third edition
LC–MS/MS	Liquid chromatography–tandem mass spectrometry
MwP	Migraine with preventive treatment
Mw/oP	Migraine without preventive treatment
PHQ-9	Patient Health Questionnaire-9
SCFA	Short-chain fatty acid

Supplementary Information

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Supplementary Material 1

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None.

Author contributions

SC conceptualized and designed the study, collected and analyzed the data, interpreted the results, and drafted the manuscript. SGL collected and analyzed the data, interpreted the results, and drafted the manuscript. HJL collected and analyzed the data, and interpreted the results. JY, WSH, and KMK critically revised the manuscript for important intellectual content. MKC conceptualized and designed the study, collected and analyzed the data, interpreted the results, and reviewed the manuscript. All authors have read and approved the final version of the manuscript. MKC, as the guarantor of this work, had full access to all of the data in the study and assumes responsibility for the integrity of the data and the accuracy of the analyses.

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Data availability

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University (IRB No. 2019-1403-005), and was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Prior to inclusion in the study, written informed consent was obtained from all the participants.

Consent for publication

Not applicable.

Competing interests

WSH serves as junior editor of The Journal of Headache and Pain. MKC serves as a board member of The Journal of Headache and Pain. MKC was a site investigator for a multicenter trial sponsored by Biohaven Pharmaceuticals, Allergan Korea, and Ildong Pharmaceutical Company. MKC received

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