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# Differences in Clinical Features and Disability according to the Frequency of Medication Use in Patients with Chronic Migraine

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**Background and Purpose** Chronic migraine (CM) has a significant impact on daily activities, and analgesic overuse is a major contributing factor to migraine transformation. Limited information is available on the functional consequences of CM stemming from analgesic overuse. This study evaluated the impact of the frequency of analgesic medication use on headache-related disability and clinical features in patients with CM.

**Methods** Patients with CM were enrolled consecutively and classified into two groups according to their frequency of medication use: <15 days/month (CM-ML,  $n=52$ ) and  $\geq 15$  days/month (CM-MH,  $n=68$ ). All patients completed a structured questionnaire concerning the clinical features of their migraine, a validated version of the Migraine Disability Assessment questionnaire (MIDAS), and the Headache Impact Test-6 (HIT-6).

**Results** The pain intensity, as measured by a visual analog scale, was greater in the CM-MH group than in the CM-ML group ( $8.5 \pm 0.2$  vs.  $7.7 \pm 0.3$ , mean  $\pm$  SD;  $p < 0.05$ ). In the disability domain, the MIDAS scores were significantly higher for CM-MH patients than for CM-ML patients ( $47.6 \pm 4.8$  vs.  $26.8 \pm 4.5$ ,  $p < 0.01$ ). The impact from migraine, as measured by the HIT-6, was greater for CM-MH patients than for CM-ML patients ( $65.6 \pm 1.0$  vs.  $62.1 \pm 1.0$ ,  $p < 0.05$ ).

**Conclusions** Our results indicate that the headache pain intensity and disability are greater in patients with CM who use medication frequently.

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**Key Words** chronic migraine, disability, HIT-6, medication overuse, MIDAS.

## Introduction

Migraine is a common disease experienced by 8-12% of the population.<sup>1-3</sup> Migraine headaches have a high socioeconomic impact since their prevalence is higher among those aged 20-50 years, who engage in vigorous social activities.<sup>4</sup> Some migraine patients develop chronic migraine (CM) through a transformative process. CM accounts for approximately 50% of all chronic daily headaches in the general population,<sup>5</sup> and has several characteristic features, including a gradual increase in the frequency of headaches, poor response to acute and preventive treatments, and increased risk of medication overuse. Although the exact mechanism underlying CM is unclear, it is

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thought that medication overuse plays an important role in the development processes. CM and medication overuse are complex and controversial issues for diagnostic classification. According to the diagnostic criteria proposed in the International Headache Society's International Classification of Headache Disorders, 2nd edition (ICHD-II),<sup>6</sup> CM can only be diagnosed after discontinuing overused medication for at least 2 months. About one-third of patients with CM exhibit concurrent medication overuse,<sup>5</sup> and so it is difficult to clearly separate CM from medication-overuse headaches in clinical practice. A more comprehensive version of the ICHD-II was recently developed in an effort to mitigate the diagnostic limitations of differentiating between CM and medication-overuse headaches.<sup>7</sup>

There has been considerable debate about the causal relationship between worsening headaches and increased frequency of analgesic use.<sup>8,9</sup> In recent years the scientifically accept-

ed view has been that analgesic overuse aggravates headache through sensitization of the pain pathway,<sup>10-12</sup> and particularly in patients with a higher frequency of headache.<sup>13</sup> Therefore, it is expected that headaches are further aggravated by analgesic overuse in patients with CM. However, few studies have investigated this topic.

CM causes a considerable number of disabilities compared with episodic migraine.<sup>14-16</sup> Headaches due to medication overuse are characterized by a poor response to treatment and are believed to cause serious social disabilities.<sup>17</sup> The negative effect of medication overuse on one's quality of life, as assessed by the 36-item Short-Form questionnaire, was investigated in patients with chronic daily headaches.<sup>18</sup> However, few studies have investigated the effect of analgesic overuse on disabilities in CM. Accordingly, the present study was designed to investigate the effect of frequent medication on the clinical features of migraine and subsequent disabilities in patients with CM.

## Methods

All of the subjects included in this study were taken from a larger pool of subjects participating in an ongoing prospective study at the Headache Clinic of the Catholic University of Korea. Consecutive patients with CM were recruited. All participants were interviewed clinically and examined physically and neurologically by an experienced neurologist. The interview used structured questionnaires to acquire detailed data regarding clinical symptoms, headache variables, disability, and medications taken for abortive treatment of their headaches.

CM was diagnosed using a revised version of the operational diagnostic criteria in the appendix of the ICHD-II.<sup>19</sup> We did not include 1) patients suffering with migraine who had taken preventive medications for their migraine before enrollment, 2) patients who had taken analgesics for a purpose other than headache, and 3) patients who had taken drugs that can affect migraine features, including beta blockers and antiepileptic drugs.

The patients were instructed to maintain their current pattern of analgesic use for their migraine attack and complete a diary at the same time on the days they suffered from a headache, over an 8-week period. Each diary booklet included questions on the characteristics of the headache, associated symptoms for each attack, and information on analgesic use. We included medications such as nonsteroidal anti-inflammatory drugs, combined analgesics, over-the-counter medications, triptans, and all other drugs used for acute symptomatic headache relief. Headache pain intensity was measured by applying an anchored visual analogue scale, with 0 representing no pain at all and 10 representing the worst pain imaginable. We classified the patients with CM into two groups depend-

ing on the frequency of medication use for headache: low frequency (<15 days/month: CM-ML) and high frequency ( $\geq$ 15 days/month: CM-MH).

The disability associated with migraine was assessed using the validated Korean-translated version of the Migraine Disability Assessment questionnaire (MIDAS).<sup>20</sup> Disability as measured by MIDAS was quantified as a total score and three impact grades: grades I and II (MIDAS score  $\leq$ 10), III (MIDAS score 11-20), and IV (MIDAS score  $>$ 21).

The impact associated with migraine was assessed using the Headache Impact Test-6 (HIT-6),<sup>21</sup> with the results stratified into four grade-based classes: little or no impact (HIT-6 score: 36-49), moderate impact (HIT-6 score: 50-55), substantial impact (HIT-6 score: 56-59), and severe impact (HIT-6 score: 60-78).

Categorical variables are presented as percentages, and continuous variables are summarized using descriptive statistics (mean $\pm$ SD). The presence of a standard normal distribution was confirmed with the Kolmogorov-Smirnov test. The clinical variables of the headaches and the total score on the MIDAS and HIT-6 were compared between the CM-ML and CM-MH groups using independent *t*-tests for parametric continuous variables. Frequency variables were compared using the chi-square test. We used the nonparametric Mann-Whitney U-test to compare continuous variables that did not fit a standard normal distribution. SPSS statistical software (version 18.0, Chicago, IL, USA) was used in all analyses. The level of statistical significance was set at  $p < 0.05$ .

This study was approved by the institutional ethics committee of our institute, and written informed consent was obtained from all participating subjects.

## Results

### Patient demographics

In total, 120 patients with CM, comprising 52 CM-ML (43.8 $\pm$ 14.1 years, 93% female) and 68 CM-MH (44.8 $\pm$ 14.0 years, 87% female), were included in the study. The age, sex ratio, and family history of headaches were same in the two groups. Medications were taken at frequencies of 20.5 days/month and 8.2 days/month in the CM-MH and CM-ML groups, respectively. Of the patients in the CM-MH group, 23.5% used simple analgesics (mean, 20.0 days/month), while 70.6% used combined analgesics (mean, 20.2 days/month), 1.5% used triptans (mean, 14 days/month), and 4.4% used caffeine-ergot (mean, 28 days/month). The duration of the migraine was longer in the CM-MH group than in the CM-ML group ( $p < 0.05$ ). The scores for the Beck Depression Inventory or Beck Anxiety Inventory did not differ significantly between the two groups (Table 1).

**Table 1.** Headache characteristics, psychiatric scales, and disability profiles for patients in the CM-MH and CM-ML groups. Except where stated otherwise, data are mean±SD values

	CM-MH (n=68)	CM-ML (n=52)
Duration of illness (years)	11.4±9.7*	6.6±5.7
Family history of headache	57.3%	27.0%
Frequency of medication use (per month)	20.5±8.2*	8.2±7.2
Duration of attacks (hours)	23.2±14.3	18.0±12.4
Headache frequency (per month)	24.0±6.7	22.1±7.0
Pain intensity (VAS score)†	8.5±1.5*	7.7±1.8
Unilateral location (%)	52.9	64.7
Pulsating quality (%)	82.4	68.6
Moderate or severe pain intensity (%)	98.5	93.6
Aggravation by ADL/ avoidance of routine physical activity (%)	67.6	56.9
Nausea/Vomiting (%)	67.6	62.7
Photophobia (%)	36.8	35.3
Phonophobia (%)	75.0	62.7
Beck depression inventory score	17.0±11.1	16.4±12.3
Beck anxiety inventory score	15.8±11.2	13.9±11.2
HIT-6 score	65.6±8.2*	62.1±6.0
MIDAS score	47.6±37.0*	26.8±26.7

\* $p < 0.05$  compared to CM-ML, †The nonparametric Mann-Whitney U-test was used to compare continuous variables that did not fit a standard normal distribution.

The frequency of medication use:  $< 15$  days/month (CM-ML) and  $\geq 15$  days/month (CM-MH).

ADL: activities of daily living.

### Clinical characteristics of migraine

Headache intensity, as measured using a visual analogue scale, was significantly higher in the CM-MH group than in the CM-ML group ( $p < 0.05$ ). Migraine frequency was also higher in the CM-MH group than in the CM-ML group, but the difference was not significant. No significant difference in distribution according to pulsating quality, unilaterality, nausea/vomiting, phonophobia, photophobia, or moderate-to-severe pain intensity was observed between the CM-MH and CM-ML groups (Table 1).

### MIDAS and HIT-6 scores

As a measure of disability due to migraine, the MIDAS scores showed that migraine was experienced for means of 47.6 days and 26.8 days in the CM-MH and CM-ML groups, respectively, indicating that those in the CM-MH group appeared to endure greater suffering. MIDAS Grade 4, representing severe disability, was observed in 73% and 32% of the CM-MH and CM-ML patients, respectively. The HIT-6 scores also differed significantly between the two groups. The weighted grade distribution showed a tendency toward severe impact in both

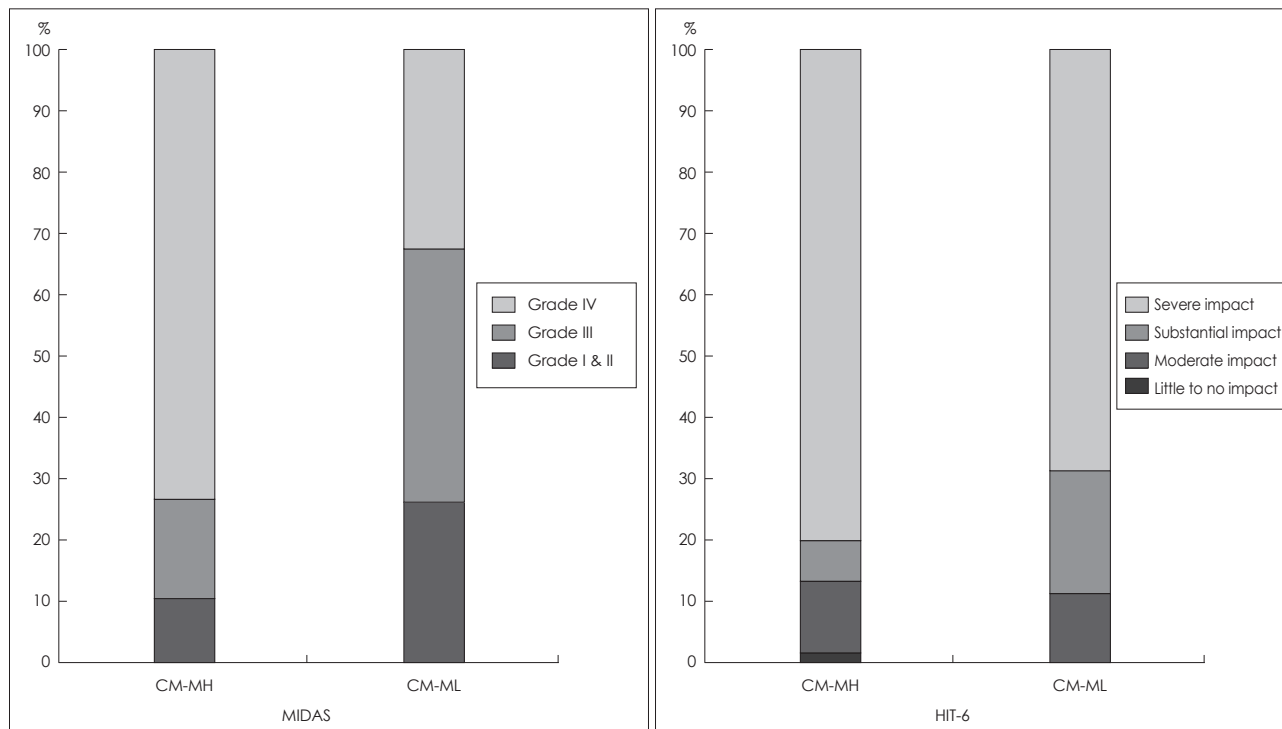
groups (Table 1, Fig. 1).

## Discussion

The present study found that the pain intensity of migraine was higher for patients in the CM-MH group than for those in the CM-ML group. While medication overuse and CM are linked, the actual causal path (i.e., whether increased frequency of medication is a cause or consequence of pain progression) remains a matter of debate. However, a considerable number of studies have demonstrated a causal role for medication overuse in headache worsening. In a study of the incidence of headaches in patients with rheumatoid arthritis who took analgesics regularly for their musculoskeletal pain, the frequent use of analgesics led to the development of chronic daily headaches in most patients.<sup>21</sup> Furthermore, headaches were significantly reduced when analgesics were discontinued among chronic headache patients who overused analgesics.<sup>22,23</sup> It has also been reported that genetic factors could influence the pattern of analgesic usage without affecting the headache characteristics.<sup>24</sup> In the present study, several points support a causal aspect of medication overuse for increased pain intensity, including 1) the inclusion of only patients with CM who already had a large number of headache attacks and 2) that the headache frequency, which could be a major factor in the decision to take medication, nausea/vomiting, and phonophobia/photophobia did not differ between the groups.

While the exact mechanisms by which analgesic overuse worsens headache remain unknown, there is evidence that it is associated with the development of central sensitization.<sup>25,26</sup> Temporal summation and wind-up phenomena as a result of repetitive pain stimuli have been shown in patients with chronic headache and analgesic overuse,<sup>27</sup> and  $\beta$ -endorphins in the cerebrospinal fluid are reduced in patients with chronic daily headache.<sup>28</sup> Pronociceptive changes occur when triptans are experimentally administered chronically to the trigeminal branch nerve endings,<sup>29</sup> and increases in calcitonin gene-related peptide and nitric oxide synthase have been observed in the trigeminal nucleus.<sup>29</sup> The induction of analgesic overuse by acetaminophen reinforced the susceptibility to cortical spreading depression and pain delivery signals through the trigeminal nucleus.<sup>30</sup> Together with this series of studies, our results suggest that frequent medication use contributes to the worsening of headaches intensity in patients with CM.

In the present study, the duration of migraine illness was longer for patients in the CM-MH group than for those in the CM-ML group. Considering the role of medication overuse in chronic daily headaches, one may reasonably assume that some patients with CM transformed to become medication overusers over time. However, clarifying this would require



**Fig. 1.** Differences in the MIDAS and HIT-6 grade distributions between the CM-MH and CM-ML groups. The frequency of medication use: <15 days/month (CM-ML) and  $\geq 15$  days/month (CM-MH). HIT-6: Headache Impact Test-6, MIDAS: Migraine Disability Assessment questionnaire.

analysis of the temporal relationship between the development of CM and medication overuse in each patient. The incomplete results obtained in the present study suggest that patients with longer histories of migraine are at an increased risk for overexposure to medication consumption.

The transformation from episodic migraine to CM depends mainly upon an increased frequency of headaches. Although contradictory opinions exist regarding the causal effect of the frequent use of analgesics on increased headache frequency,<sup>12,31-33</sup> it is accepted that analgesic overuse plays an important role in increasing the frequency of migraine attacks and the transformation into CM. The present study found that headache frequency did not differ between the CM-MH and CM-ML groups, which makes it difficult to conclude whether the frequency of medication use contributed to the increased headache frequency observed in our CM patients. The possibility of a ceiling effect on headache frequency in migraine patients who have already developed chronic daily headaches should be considered. Further study of a larger sample of patients is required to clarify this issue.

In the present study, the patients in the CM-MH group reported greater disability and were more likely to have a severe MIDAS grade. The MIDAS score is a useful tool for objectively evaluating reduced productivity by documenting the days of poor performance in the school/workplace/home due to headaches over a 3-month period.<sup>20</sup> Several studies have

consistently found increased disability and reduced productivity in patients with chronic daily headaches compared with patients with episodic migraine.<sup>16,34,35</sup> This supports the supposition of the present study that MIDAS scores are increased in patients with CM who use medication frequently. The increased disability could be a reflection of the difference in pain severity between the groups. The present study found no significant difference in headache frequency or the severity of depression and anxiety between the groups, conditions that are known to have a considerable effect on disability. However, it is not possible to conclude unequivocally that the difference in pain severity was the sole source of the greater disability in patients with CM, because the results of previous studies showing that pain severity contributed independently to disability are inadequate.<sup>35</sup>

The HIT-6 impact score was also found to be significantly higher for patients in the CM-MH group than for those in the CM-ML group. Since the actual difference in HIT-6 scores did not seem to be large, caution should be applied to the clinical interpretation of these data. The distribution of HIT-6 scores was narrow, and most patients in both groups of CM sufferers were included in the severe grade; hence, the discrimination power may have been inadequate. MIDAS scores might be a more suitable measure of disability than HIT-6 scores in CM patients who overuse medication.

A limitation of this study was that the frequency of medica-

tion use in patients in the CM-MH group can also be applied to diagnostic criteria of medication-overuse headache. In the revised version of the ICHD-II, which was used to classify the patients in this study, CM should be diagnosed in cases of the absence of medication-overuse headache. From a clinical perspective it is possible that some patients in the CM-MH group did not experience medication-overuse headaches because of their frequent migraine attacks. Thus, that we did not exclude all such patients in this clinical study of CM is an additional limitation. Furthermore, it is difficult to clarify a direct temporal relationship between medication overuse and worsening of headache in patients with CM. An additional study with strict selection of patients who overuse medication is required.

The present study has revealed that patients with CM and frequent medication use experience greater pain intensity and disability. This finding suggests that the strict regulation of medication use in patients with CM will decrease the degree of disability and improve the productivity in this population, leading to a reduced socioeconomic burden.

#### Conflicts of Interest

The authors have no financial conflicts of interest.

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