ORIGINAL ARTICLE

Medication overuse headache and its specific clinical markers

Cefaleia por uso excessivo de medicação e seus marcadores clínicos específicos

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ABSTRACT

Introduction: Clinical markers of medication overuse headache (MOH) are based on headache classification developed by the International Headache Society (IHS). This classification include only two criteria: 1) frequency of headache must be 15 or more days per month for at least three or more months; 2) the number of days of overuse medication must be either 10 or 15 days per month depending on the type of medication. However, patients often present with associated clinical markers that are overlooked by most physicians at the first visit. Methods: This is a prospective, longitudinal and observational study of 76 patients admitted to DIPRECA´s hospital Headache Unit. They were all diagnosed with MOH according to the criteria established by the his ICHD III beta. Patients were given standard therapeutic approach that included detoxification, prescription of preventative medications and a standardized follow-up of 6 months. Symptoms of interest were recorded at each appointment and Zung, MIDAS and HIT-6 (headache impact test) scales were applied. Results: Overused medications included nonsteroidal anti-inflammatory drugs (NSAIDs), triptans and ergots. The most significant associated features were headache at awakening, awaking by headache, attentional difficulties, depression, cervical pain and myofascial pain syndrome. All symptoms improved with therapy as well as MIDAS and HIT-6 scores. Discussion: In evaluating patients with MOH consider both the ICHD III beta diagnostic criteria and the common and specific symptoms seen in most cases of MOH.

Keywords: Medication overuse headache, Chronic migraine, ICHD-III beta, Depression, Early morning awakening headache, Quality of life, MIDAS, HIT-6.

INTRODUCTION

Medication overuse headache (MOH) is a secondary headache usually seen in patients with chronic daily headache (CDH), in whom most meet diagnostic criteria for chronic migraine. These patients usually have 15 or more headache days in which the episodes last at least 4 hours a day for three months or longer. In addition, they must be taking analgesic medication(s) for at least 10 or 15 days per month depending on the medication.[1,2,3] Chronic daily headache reaches a prevalence of 4-5% in the United States.[4,5] The annual incidence of new onset chronic migraine (CM) in patients with episodic migraine (EM) averages 2.5%[6,7] and MOH prevalence in the general population is estimated to be of 1-2%, mostly affecting women. At dedicated headache centers, MOH accounts for 70% of the new patients or more.[4,3] A survey by Rapoport showed that MOH has become the third most common cause of headache in the United State,[8] a relevant aspect since of its high socio-economic impact.[2,4,9]

A meta-analysis revealed that the most frequent headache diagnoses in patients with MOH were migraine (65%), tension-type headache (27%) and migraine associated with other headaches (8%).[10] Other studies confirmed migraine to be the most common headache that precedes MOH.[2,4,3] In the United States, triptans in conjunction with opioids were the mostly abused headache drugs, in spite of the widespread use of NSAIDS and/or butalbital containing

medications.[11] This pattern of headache drug abuse was not found in other headache populations.[4]

Regardless of the initial headache syndrome or the specific medication being overused, the mainstays of our treatment are: 1) detoxification from the overused medication, 2) non-pharmacological and 3) pharmacological preventive treatment, with 4) proper use of symptomatic medications.[12,13] Patients with MOH have MIDAS scores three times higher as compared to those who have episodic migraine who are not overusing medications.[2,14] MOH patients also have an increased risk of mood disorders and anxiety.[15-18] Sleep disorders are more frequent among patients with MOH that in those presenting episodic headaches.[19]

It is usually agreed that by most headache specialists that an structured approach for treating MOHs includes: a) educating patients to stop taking the medicine abused (day 1), b) detoxification from the overused medications with the help of an antiemetic and analgesic, if needed (days 1-7), c) institution of a preventive medicine between days 1-7, d) prescription of an appropriate use of analgesics and e) follow-up visits for at least six months.[20,21]

Preventive medications considered useful are valproate,[21-23] topiramate,[21,24,25] onabotulinumtoxinA[21,26] and quetiapine, the last one used as an add-on therapy during detoxification.[27]

While treating MOH, a treatment can be considered as successful if a reduction in the headache days of 50% or more is attained after 3 months of therapy. [9]

Success rates of MOH therapy are reported to fall around 70%. These results are commonly based on in-patient treatment, rescue medication and continued support. In addition, the 70% success rates reported were based on different outcome measures and therefore difficult to compare.[28]

Some factors that appear to negatively affect the results are the high use of medicines at the beginning of detoxification, the reuse of previously abused drugs, failure to improve after two months of treatment, smoking and alcohol use. Although psychiatric comorbidities are not related to relapse after one year of treatment, those patients with lesser depression and/or anxiety scores had better results after four years of detoxification.[4,16-18] Treatment of MOH undoubtedly has a positive impact on the quality of life of these patients.[29,30]

OBJECTIVES

To determine the following in patients with MOH: headache frequency and intensity, if the patient awakens in the morning with headache, if the patient is awakened at dawn by headache, inattention, depression, cervical pain and myofascial pain syndrome.

To describe the evolution of these symptoms during the 6 month follow-up and their impact on quality of life in relation to treatment.

MATERIAL AND METHODS

The present study was approved by the Ethics and Research Committee of DIPRECA Hospital and all patients were fully informed and agreed to participate in the study. Patients allowed the use of their medical record data and gave consent regarding the use of their clinical records for research purposes, anonymously.

This was a prospective, longitudinal observational, study on 76 consecutive patients who met the IHS criteria for medication overuse headache. They were admitted to DIPRECA´s Hospital Headache Unit between March 2014 and April 2015. Patients were given follow-up neurological evaluations at month 1, 2, 3 and 6.

During the initial evaluation, relevant clinical data were considered and recorded in a standardized record, including headache frequency and intensity as recorded on a visual analog scale (VAS), medication use and overuse, awakening times and reasons, attention difficulties, cervical pain and myofascial pain syndrome.

The Zung scale was used for evaluation of depression and the MIDAS and HIT-6 scales for evaluation of disability and impact on quality of life.

For statistical analysis, parametric tests the 2 test, and nonparametric Student t test, with the SSSP program were used.

The detoxification and treatment protocol used in our Headache Unit at DIPRECA Hospital consists of suspension of the overused medication and initiation of a joint pharmacological support therapy during the first 3 months.

In the first month we attempt an ambulatory therapy, utilizing different medications from those overused by the patient. We use injectable NSAIDs, not to exceed 2 vials of diclofenac 75 mg IM, secondly oral quetiapine 25 mg/day, and then treatment with sodium divalproex ER 500 mg daily for 3 months as a preventive approach. An alternative treatment is onabotulinumtoxinA 100 IU, within the first 2 weeks of treatment.

During the second and third months of treatment injectable NSAIDs were replaced by oral analgesics if necessary, not to exceed 10 days of use per month, while maintaining the use of quetiapine and divalproex sodium ER in the same dose for 3 months.

If progress is satisfactory, an assessment to decide whether to maintain treatment during the third month is made and monitoring continues.

RESULTS

A total of 76 patients met the diagnostic criteria for MOH, all consented to the present study, all received detoxification treatment, and all completed 6 months of follow-up for this study.

The demographic characteristics of the study population reveals an average age of 41.17 years (16-68), with a female predominance (80.26%). The average length of painkiller overuse was two years, but for some patients over a decade. Nine of our patients had a history of prior MOH treatment (11.8%), with little use of preventive drugs. Among the significant comorbidities overweight, obesity and depression are highlighted. (Table 1 and Table 2)

Table 1. Demographic characteristics

Mean age	41.17 years (16-68)
Female	80.26% (61)
Male	19.74% (15)
Migraine without aura	100% (76)
Migraine with aura	2.7% (2)
Migraine in family	68.42% (52)
Months of overuse	23.9 (5-180)
History of previous detoxification	11.84% (9)
Use of preventive medication	9.21% (7)
Previous onabotulinumtoxin A	0% (0)

Table 2. Comorbidities

Characteristics	% (n)	Characteristics	% (n)
Obesity	10.5 (8)	Depression	31.57 (24)
Overweight	42.1 (32)	Anxiety	11.84 (9)
BMI	24.8 (18-34)	Epilepsy	1.31 (1)
HTA	11.84 (9)	Vertigo	6.57 (5)
DM2	5.26 (4)	Insomnia	26.31 (23)
Dyslipidemia	5.26 (4)	Restless legs syndrome	2.63 (2)
Hypothyroidism	11.84 (9)	Sleep apnea	3.95 (3)
Coronary artery disease	1.31 (1)	Tobacco use	11.84 (9)

Overused Medications

The most overused medication were the nonsteroidal anti-inflammatories (NSAIDs) (84.21%), followed by ergots (35.52%), triptans (34.21%), the combination of NSAIDs with ergots (14.47%), or triptans (15.78%). This seemed representative of the situation of patients nationwide, according to the clinical experience of the authors. This group of patients was remarkable for their low use of opioids and barbiturates. (Figures 1 and 2)

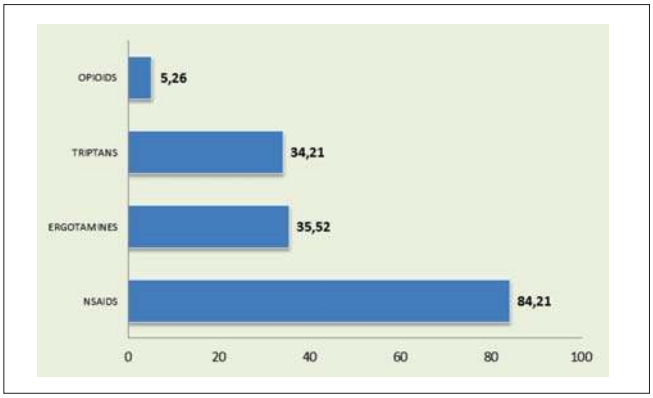


Figure 1. Medications overused

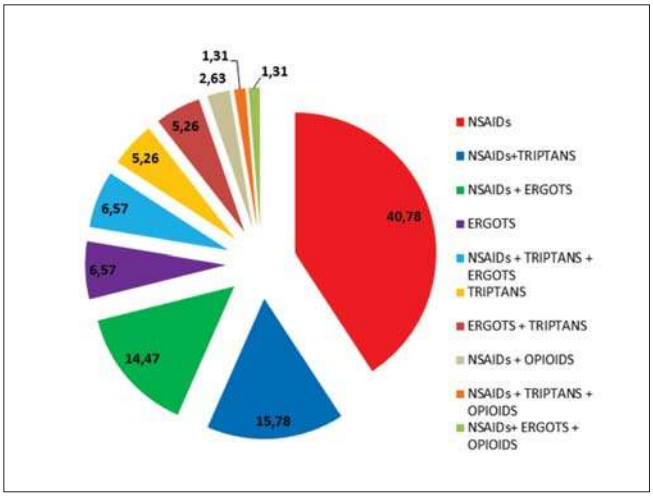


Figure 2. Mix of medications overused

Frequency of headache attacks

Regarding the frequency of headache attacks during the initial evaluation of our patients, we found an average of 22.25 days of headache per month (range between 15 and 30 days of pain), with a gradual decrease in frequency after the initiation of therapy and discontinuation of the overused drug. There was a statistically significant reduction in headache frequency, as compared to the initial frequency, for each assessment during follow-up (95%, Paired sample test, $p < 0.001$); this reached a minimum of 3.86 average headache days in the third month, which was maintained during the sixth month of monitoring. There was no statistical difference when comparing the frequency between the third and sixth months (95% CI, Paired sample test, p 0.321). It is noteworthy that only 2 patients persisted with an attack

frequency of greater than 15 days per month at 3 months follow-up, and 9 patients were actually headache free at 6 months follow-up. (Figure 3)

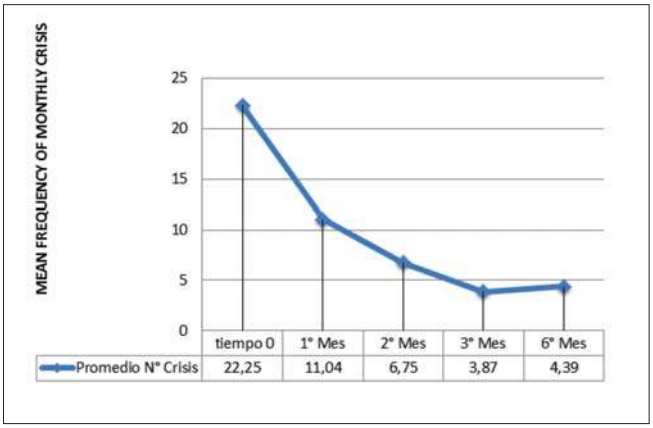


Figure 3. Average of headache frequency during follow-up

Headache Intensity

There was a progressive decline in the intensity of pain during headache crises, highlighting a mean baseline intensity of 7.3±1.2, decreasing to 5.2±1.5) at 1 month, to 4.1 (SD 1.8) at 2 month, to 3,1±2.1 at 3 month and to 2.7±2.7 at 6 months, respectively. The average pain intensity decrease was statistically significant from the initial intensity (Paired sample test, $p < 0.001$) with no significant difference comparing the third and sixth months. (Figure 4)

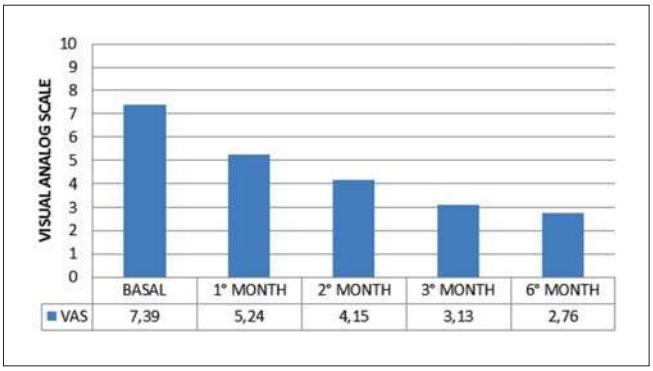


Figure 4. Headache intensity

Other Clinical Symptoms

During the initial evaluation of patients, almost all patients reported waking up with headache in the morning. This was followed in frequency by being awakened by headache at dawn and myofascial pain syndrome, difficulties in attention, neck pain, and psychiatric comorbidities such as depression (assessed by the Zung scale). These findings are presented in Figure 4.

Waking up in the morning with headache

As Figure 4 shows, waking up in the morning with headache was the most frequently reported symptom before detoxification treatment began and it decreased progressively once management of MOH was initiated.

This symptom was reported at the initiation of the study in 98.7%, at the end of the first month in 50%, at the end of the 2nd month in 30.7%, at the end of the 3rd month in 14.7% and at the end of the 6th month in 21%. The difference was significant comparing initiation and month 3. (χ^2 $p < 0.001$)

This headache is typically mild and located in frontal and periorbital areas. (Figure 5).

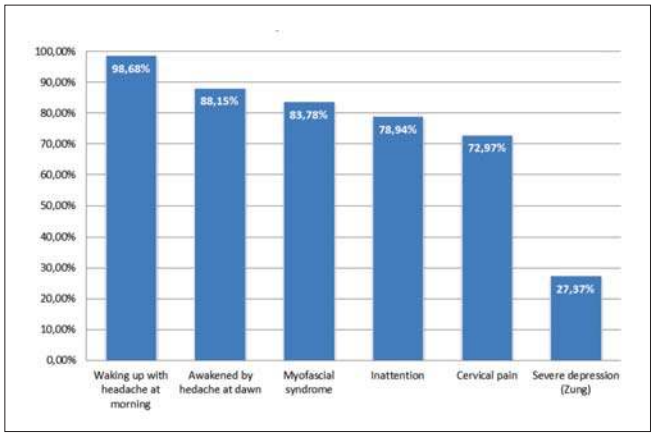
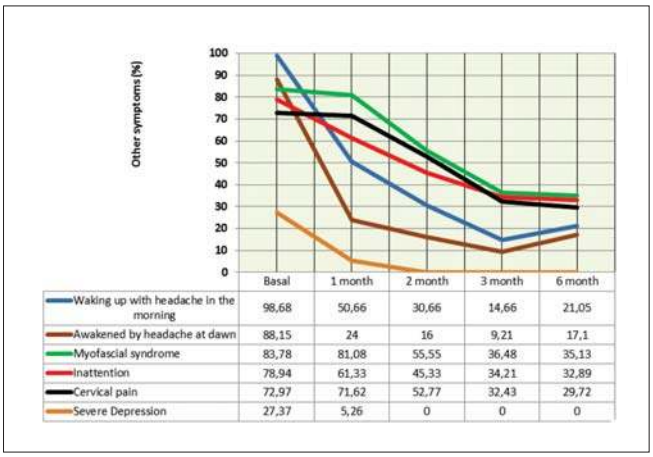


Figure 5. Acompanying symptoms in the first evaluation

Being awakened at dawn by headache: Being awakened at dawn by headache is a frequently reported symptom in patients with MOH. In this series it is the second most frequently observed symptom, seen in 88.15% of patients on study entry, and improving to 24% at the end of month 1, 16% at month 2, 9.2% at month 3 and 17.1% at month 6; this was significant when compared to baseline (χ^2 test, $p < 0.001$), and not significant comparing month 3 and 6. This headache is typically holocraneal and always severe and 76% of the patient are headache free by the 1st month. (Figures 5 and 6).

Cervical Myofascial Syndrome

The cervical myofascial syndrome is a non-inflammatory disorder manifested by localized pain and stiffness, associated with trigger points and limited cervical movement. The three basic components of this syndrome include: a palpable band in the affected muscle, the presence of trigger points and referred pain patterns. It was clinically evaluated for each patient by history and physical examination. Myofascial pain was also frequently reported



	Basal	1 month	2 month	3 month	6 month
Waking up with headache in the morning	98,68	50,66	30,66	14,66	21,05
Awakened by headache at dawn	88,15	24	16	9,21	17,1
Myofascial syndrome	83,78	81,08	55,55	36,48	35,13
Inattention	78,94	61,33	45,33	34,21	32,89
Cervical pain	72,97	71,62	52,77	32,43	29,72
Severe Depression	27,37	5,26	0	0	0

Figure 6. Changes in symptoms during follow-up assessments

by these patients: at the start of the study 83.78% (61 patients) had myofascial pain, decreasing to 81.08% (60 patients) at 1 month follow-up, 55.55% (40 patients) at 2 months, 36.48% (27 patients) at 3 months and 35% (26 patients) at 6 months. A response was seen after treatment initiation with statistically significant differences from baseline to 6 month (95 % χ^2: $p < 0.001$). (Figure 6)

Cervical Pain

Neck pain as a separate symptom from myofascial syndrome is assessed by the patient's history during the interview, and is also a common symptom in these patients. Prior to initiation of treatment 72.97% (54 patients) reported neck pain, and a significant decrease during follow-up assessments was noted. During the first month 71.62% (53 patients) had neck pain, 52.77% (38 patients) at month 2, 32.43% at month 3 and 29.72% at 6 months. (Figure 6) Statistically significant differences were noted comparing baseline to 6 months (95% χ^2: $p < 0.001$).

Attentional Difficulties

Difficulty in sustaining a focus of attention on a particular task is also common among these patients. To evaluate this symptom we asked the following questions in relation to the three months prior to the first visit: "Have you noticed more difficulty in sustaining attention regarding tasks that require sustained mental effort?", "Are you easily distracted by minor stimuli?", " have you noticed major difficulty in completing work related tasks or during other entertaining activities?", "Are you more forgetful than before?"

The presence of inattention was considered as an affirmative response to any of the questions above. Initially 78.94% (60 patients) reported attention problems, at the end of the first month 61.33%, 45.33% at month 2, 34.21% (26 patients) at month 3 and 32.9% (25 patients) at month 6. There was a statistically significant difference from baseline at month 6 (95% χ^2: $p < 0.001$). (Figure 5).

Depression

In order to evaluate depression we used the Zung Scale abbreviated and validated for South American populations.[31] This validated version established the *cutoff* for mild depression at 15-20 points, 23-24 points for mild for moderate depression, 21-27 for moderate depression and 27-40 points for severe depression.

At the initial assessment 41 patients had scores of 24 or more points (53.9%) and 21 patients (27.37%) had severe depression, with an average score of 24.41±5.226 points. At baseline, severe depression was detected in 27.37% of the sample, in 5.56% after one month of protocol and in 0% of the sample at months two, three and six. Within the first month the average depression score was 20.11±4.61, after months 18.49±4.82, 16.24±4.68 after three months and 16.71±5.61 at 6 months. The last 3 values were under the cutoff for depression.

Comparing the average values between the different months up to month 3, there is a statistical difference in all of them, as compared to baseline (95% CI Paired sample test Sig two-tailed p <0.000), with no statistical difference between the sixth and third month (p 0.363). (Figure 5)

Quality of Life

In order to evaluate quality of life we used the MIDAS and HIT-6 scales, which are broadly used and validated for this purpose.[32,33] Both scales demonstrated a poor quality of life during the baseline assessment, with a fall in its severity once detoxification treatment began. In regard to the MIDAS scale, a larger grade signifies a worse quality of life with more disability (Grade I: 0-5 points; Grade II: 6-10 points; Grade III: 11-20 points; Grade IV: 21 or more points). This scale was evaluated at baseline and at months 3 and 6.

The average score for all patients (n = 76) at initial evaluation was 72.08±60.58 points, falling to 14.39±13.33 at month 3 and 11.96±18.51 at month 6, There is a significant difference when comparing the baseline value with the average of 3 to 6 months (95% CI, Paired sample test, p <0.0001), and no differences between the third and six months (95% CI, Sig. 2-tailed 0.106). By classifying the severity of the alteration of quality of life we found 93.42% (71 patients) with severe limitations and need for treatment (Grade IV) at baseline, and only 15.4% (12 patients) in this category by 6 month follow-up. None

of the patients evaluated had scores for grade I on the MIDAS scale (minor limitations and no needs for treatment) in the initial assessment; however, 25% (n=19) and 52.3% (n=39) were qualified as grade I at 3 and 6 months, respectively. In Figure 7 the changes obtained in the evaluation of this scale can be observed during follow-up.

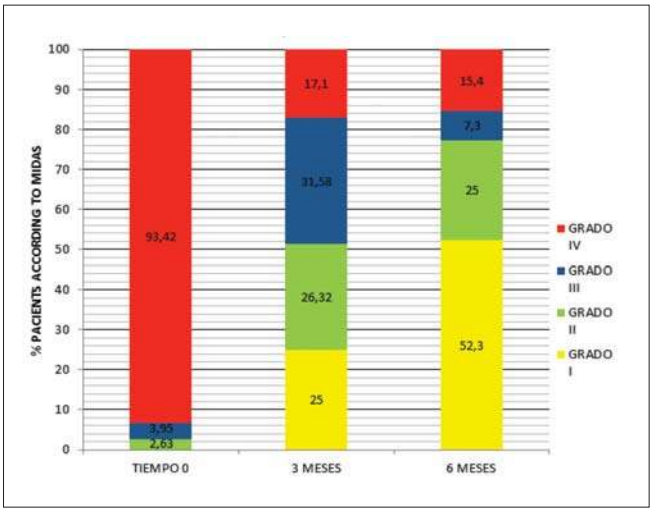
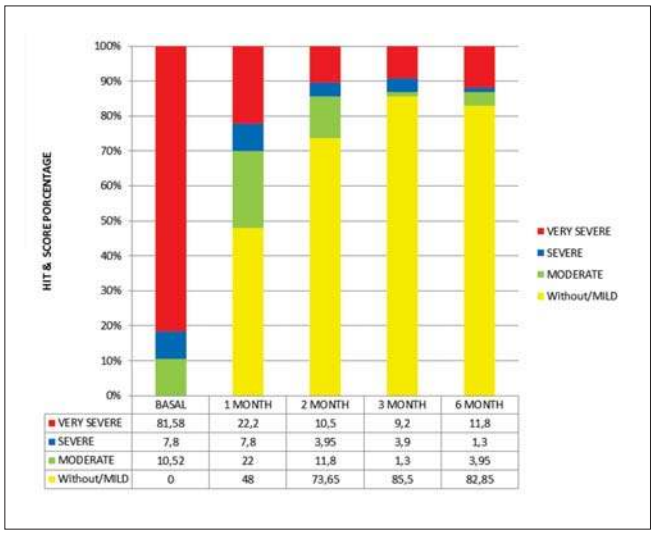


Figure 7. MIDAS Score

The results obtained with the HIT-6 scale are similar to those obtained with the MIDAS scale. The HIT-6 scale categorizes the results according to severity: very severe (60 or more points), severe (56-59), moderate (50-55) and mild or no impact (36-49). The average of all patients in the initial evaluation of the HIT-6 was 65.5±6.675 points, falling to 51.15±8.52 at the first month, 45.75±9.75 at the second month, 41.3±10.48 at the third month and 41.2±12.23 at the sixth month.

There were statistically significant differences when comparing results from baseline. (Paired sample test, 95% next 2-tail; p <0.001), with significant differences also between the months 1, 2 and 3 of follow-up (p <0.001), but with no statistical difference when comparing the third and sixth month (p 0.175).

To categorize patients according to severity in the first evaluation 81.58% (n= 62) were "very severe," 7.8 (n= 6) "severe" and 10.5 score (n= 8) "moderate" noting that no patient fulfilled score for "slight or no impact on their quality of life". As with the MIDAS scale, we can see a progressive increase in mild or no impact category (quality of life) after treatment started, with 65 (85.5%) and 63 (82.25%) patients reaching the mild category at 3 and 6 months, respectively; there was a significant drop in the number of patients with severe alterations in quality of life, with only 7 (9.2%) patients in this category at 3 months follow-up. (Figure 8).



	BASAL	1 MONTH	2 MONTH	3 MONTH	6 MONTH
VERY SEVERE	81,58	22,2	10,5	9,2	11,8
SEVERE	7,8	7,8	3,95	3,9	1,3
MODERATE	10,52	22	11,8	1,3	3,95
Without/MILD	0	48	73,65	85,5	82,85

Figure 8. HIT-6 Score

DISCUSSION

Traditionally the diagnosis of MOH is made based on the criteria set by the diagnostic classification of the IHS, which basically takes into account the headache frequency parameter (more than 15 days per month) and the number of days of medication overuse, as well as the type of medication. However, in clinical practice patients report additional symptoms, namely awakening in the morning with headache, being awakened at dawn by headache, depression, inattention, cervical pain and myofascial pain syndrome. These symptoms, despite not being included in the diagnostic criteria, aid in the clinical evaluation process and the monitoring of patients during the treatment of this disease.

This paper demonstrates that the symptoms described above are frequently observed in patients with MOH, as they are seen in over 80-90% of patients. As such, we consider them of great importance in strengthening the IHS criteria and achieving greater accuracy and usefulness in following outcomes during the management of this condition.

There are specific situations that may result in early diagnosis of MOH, such as patients who overuse medication, have a lower frequency of headaches than the 15 days a month that the IHS criteria requires, but demonstrate some of the symptoms described above. Early diagnosis can lead to initiation of early treatment. The same situation pertains to patients with chronic headache who do not meet the criteria for medication overuse described in the IHS criteria. In the authors' opinion these clinical markers, specific to MOH, such as waking up in the morning with headache, being awakened at dawn by headache and the myofascial

syndrome, are frequent occurrences and quite specific for MOH. Depression, neck pain and inattention are comorbidities, but helpful in combination. We suggest that these symptoms we have delineated should be further evaluated and possibly be included in MOH diagnostic criteria in future ICHD versions.

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