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Hartmut Göbel, Axel Heinze

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The Migraine Intervention Score (MIS) - a tool to improve efficacy of triptans in acute migraine therapy: The ALADIN study

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The Migraine Intervention Score (MIS) - a tool to improve efficacy of triptans in acute migraine therapy: The ALADIN study

Hartmut Göbel and Axel Heinze

Kiel Headache and Pain Centre, Schmerzlinik Kiel, Kiel, Germany,

Address for correspondance

Hartmut Göbel
Kiel Headache and Pain Centre
Heikendorfer Weg 9-27
D-24149 Kiel - Germany
Tel: +49 431 200 99 150
Fax: +49 431 200 99 109
E-mail: hg@schmerzklinik.de

Abstract

Background: The "Migraine Intervention Score" (MIS) is a new self-administered scale that can be used to quantify the severity of specific migraine symptoms. The objective of the present study was to determine if MIS could be used to improve the efficacy of frovatriptan 2.5 mg in the early treatment of migraine attacks for clinical practice.

Methods: In this prospective, observational study patients suffering from migraines with or without aura were enrolled and permitted to choose the time of self-medication with frovatriptan 2.5 mg. At the time of intake of medication, patients evaluated the severity of individual migraine symptoms using MIS. The scores for each symptom were then totalled to provide an overall level of symptom severity. A total of 1620 patients completed the treatment of 3 migraine attacks with frovatriptan. 1518 patients could be analyzed with respect to the documented efficacy parameters of the third attack. Patients initiating treatment at low symptom severity levels were compared to those initiating treatment at high symptom severity levels.

Results: Time to the achievement of the primary endpoint (headache response) was significantly lower in patients who initiated treatment at low versus high symptom severity levels (42.06 ± 32.33 vs. 49.25 ± 34.92 min; $p=0.0023$). Likewise, patients who initiated treatment at low symptom severity levels achieved complete headache relief more rapidly (79.37 ± 65.33 vs. 96.05 ± 100.85 min; $p=0.0109$) and required escape medication less frequently (3.88% vs. 13.73%; $p<0.0001$).

Conclusions: The initiation of attack treatment with frovatriptan at low severity of migraine symptoms is more effective than starting therapy at higher symptom levels. Together with the low recurrence headache rate, the decreased necessity for escape medication and the low number of tablets needed, these data demonstrate that operationalized intervention with frovatriptan 2.5 mg is a valuable method for improving the treatment of migraine attacks.

Keywords:

Migraine treatment, Frovatriptan, onset of action, intervention at low severity levels of migraine symptoms

What's already known about this topic?

In primary care setting, early intervention with some triptans for treatment of migraine provides significant clinical benefits compared with delaying treatment and/or waiting until pain intensity has progressed beyond mild.

What does this article add?

The study shows in clinical practice for the first time using a new self-administered scale that frovatriptan taken at an early stage with mild headache and accompanying symptoms lead to earlier treatment response and more rapid headache relief than treatment initiated when symptoms were more severe.

Background

Migraine is a highly prevalent, chronic neurological disorder that is often associated with severe disability; this places considerable burden on both the individual and society[1]. The World Health Organization ranks migraines at 19th place among diseases that cause severe disabilities [2-5]. Migraine attacks typically last from 4 to 72 hours, and are characterized by recurrent episodes of headache and associated symptoms such as one-sided localization, pulsating pain of a moderate-to-severe intensity, aggravation from daily physical activities, nausea, and light or noise hypersensitivity [2, 4, 6-8].

The introduction of selective 5-HT_{1B/1D} receptor agonists marked a milestone in the treatment of acute migraine attacks, and data from clinical studies have shown them to be a highly-effective and specific treatment option for acute migraine attacks [9, 10]. In general, triptans are taken during the course of an attack when the patient is suffering from moderate or severe pain [10]. Treatment during this period increases the diagnostic certainty of a migraine attack, and often results in an improvement from a high starting level of pain intensity to a level of mild or no pain, which can be reliably measured [11].

Despite the advantages of treatment during the course of an attack, clinical experience has shown that patients benefit to varying degrees from treatment with triptans [10-12]. For example, a treatment response may develop later in some patients, which can prolong the time that is taken to achieve headache relief. In addition, the onset of headache recurrence may require the medication to be taken again, and an inadequate response to the medication may result in the use of a escape medication. In face of these issues, early treatment during a migraine attack has been investigated, and recent studies have shown that the use of triptans during periods of mild pain intensity and/or in the early attack phase can lead to improved therapeutic results [10, 11, 13].

However, pain intensity is only one characteristic of migraine attacks, and symptoms can vary widely, with a delayed onset of pain [14]. As a result, patients are generally unable to self-medicate solely on the basis of their current pain intensity. An attack may begin with nausea

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3 and/or sensory hypersensitivity, and pain may initially be perceived as a dull pressure, which
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5 is not a specific symptom of migraines. This can lead to diagnostic uncertainty as to whether a
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7 migraine attack is actually beginning or if other problems such as a tension headache are
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9 developing, for which a triptan would not be useful. Patients with very frequent attacks also
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11 need to be careful about rapid self-treatment with acute medication so that the maximum
12
13 monthly dosage is not exceeded. The advantages of early treatment include greater and more rapid
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15 efficacy [9, 11, 13, 15-31]. In addition, cutaneous allodynia may develop over the course of the attack,
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17 reducing the efficacy of triptans. For these reasons, pain intensity levels alone may not be sufficient to
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19 make decisions about triptan self-medication [32, 33, 34]. Furthermore, caution must be taken by
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21 patients with frequent attacks to ensure that rapid self-treatment with acute medication does
22
23 not lead to the maximum monthly dosage being exceeded. Therefore, it is unclear when
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25 triptan therapy should be initiated, and the issues described above indicate that pain intensity
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27 levels alone may not be sufficient to make decisions about triptan self-medication [12, 16].
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33 For many diseases, the time at which interventional treatment is initiated is determined by an
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35 operationalized measurement system. For example, treatment with antipyretics can be
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37 operationalized based on body temperature. Analogous to this, we have developed the
38
39 “Migraine Intervention Score” (MIS) to quantify the severity of migraine attack symptoms.
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41 This scoring system assigns numbers to individual migraine symptoms during the headache
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43 phase based on the International Headache Society (IHS) classification. Therefore, the overall
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45 severity of symptoms can be quantified with numeric values between 0 and 10, and the sum
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47 of scores for individual symptoms serves as a tool for migraine patients that allows for
48
49 improved identification of acute migraine attacks. In addition, trigger levels at which
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51 treatment is initiated can be determined on an individual basis and the efficacy of attack
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53 treatment can be monitored individually in relation to the severity of migraine symptoms.
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55 This allows for individual identification of optimal times for self-treatment based on the
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57 severity of symptoms and helps to prevent triptans from being taken too early or too late.
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3 To provide further insight into the timing of triptan therapy, the present study evaluated the
4 efficacy and safety of frovatriptan 2.5 mg in a very large patient group under everyday
5 treatment conditions [10, 35-37]. The study also used the MIS to determine if frovatriptan use
6 at an early stage with mild attack symptoms would lead to earlier treatment response and
7 more rapid headache relief than treatment initiated when symptoms were more severe.
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13 14 15 16 17 18 **Methods**

19 20 21 22 **Patients**

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24 We enrolled patients aged between 18 and 65 years who had an established diagnosis of
25 migraine without aura or migraine with aura as defined by IHS criteria [8] in the study.
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27 Patients were eligible if their age at migraine onset was under 50 years and if they had at least
28 one migraine attack per month and less than 10 days of non-migraine headaches per month
29 for the three months prior to study entry. In addition, patients were enrolled only if they were
30 able to distinguish migraine from non-migraine headaches. Women of childbearing potential
31 were required to use a reliable method of birth control. Patients were excluded from the study
32 if they had contraindications to frovatriptan use, which included a history or symptoms
33 suggestive of ischemic heart disease or any other vascular disease, uncontrolled hypertension
34 (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 90 mmHg) or clinically
35 significant ECG abnormalities. Patients with basilar or hemiplegic migraine or other serious
36 neurological conditions associated with headaches were also excluded.
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55 56 **Study Design**

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58 The “*Allegro-Anwendung Durch Interessierte Neurologen*” (ALADIN) trial was a post
59 marketing surveillance study, conducted under formal guidelines for company sponsored
60 safety assessment of marketed medicines at 578 investigational sites in Germany.

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3 Migraine headache was diagnosed by practicing outpatient neurologists and pain specialists.
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5 The severity of migraine symptoms was quantified using the Migraine Intervention Score
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7 (MIS). The MIS consists of the following items: pain severity (severe=2, moderate=1, low=0
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9 points), pain localization (unilateral=2, bilateral=0 points), pain character (stabbing or
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11 pulsating=2; dull pressure=0 points), pain aggravation with physical activity (yes=1, no=0
12
13 points), nausea or vomiting (yes=2, no=0 points), light or noise sensitivity (yes=1, no=0
14
15 points). The sum of these items provides a score between 0 and 10, which determines the
16
17 severity of migraine symptoms. This was calculated at the time of self-medication.
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19 Patients were permitted to choose the time of self medication, which consisted of frovatriptan
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21 tablets at the recommended dosage of 2.5 mg [35, 37]. If the migraine symptoms recurred,
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23 patients were permitted to take a second dose 2 to 24 hours later. Escape medication was
24
25 permitted, and could be started 2 hours after the first dose of study medication. The patients
26
27 were allowed to treat up to three migraine attacks during the study period; the third attack
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29 treated was evaluated in this study. At the end of the treatment period, patients returned to the
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31 study centres for review of their attack records, assessment of any adverse events and end-of-
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33 study evaluation. Attack record data and neurologist and patient ratings at the clinic were
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35 entered into case report forms.
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42 Efficacy and Tolerability Assessments

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44 Response to treatment was recorded by the patients in an attack diary. Since patients were
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46 permitted to choose the time of self-medication, "headache response" could not be defined by
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48 the conventional measure of reduction in migraine intensity from moderate or severe to mild
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50 or no pain [10]. Therefore, the primary efficacy parameter as a function of triptan threshold
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52 score was "headache response" after the initial dose of study medication, which was defined
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54 as the length of time (in minutes) between medication consumption and the onset of headache
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56 relief: Patients were asked to record the "*point in time at which the medication started to*
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58 *work*". The length of time between medication and onset of effects was defined as the
59
60 "headache response". Secondary endpoints included: the time taken to achieve complete

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3 headache relief; the incidence of headache recurrence within 24 hours (return of migraine
4 headache within 24 hours of the initial treatment after having achieved a “headache
5 response”); the number of frovatriptan tablets required to treat each attack; and the use of
6 escape medication and an evaluation of the efficacy of this medication. Patient safety was
7 assessed by clinical observation, while tolerability was assessed by recording adverse events.
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14 15 16 Statistical Analysis

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18 Baseline characteristics of the sample were compared for homogeneity across both groups.
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20 Using the split half method, patients were divided into two groups: low MIS values (severity
21 of 1-5) and high MIS values (severity 6-10). All efficacy analyses were performed on the
22 intent-to-treat (ITT) sample, defined as all subjects who took at least one dose of study
23 medication for treatment of the last migraine attack, and had one valid baseline and post-
24 baseline evaluation. Formal statistics of treatment differences for the primary and secondary
25 endpoints were calculated using a two-sided Student’s t-test with a significance level of $p \leq$
26 0.05. Differences in the percentages of patients between treatment groups were assessed with
27 the χ^2 -test.
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42 Results

43 Patient Characteristics

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46 A total of 2160 patients were included in the study, and 1620 of these patients recorded the
47 treatment of three migraine attacks during the study period. The attack record of the third
48 attack was completed by 1518 patients. According to the MIS scale, 258 patients (17%)
49 initiated self-medication with frovatriptan at low symptom severity levels (severity 1-5) and
50 1260 patients (83%) initiated self-medication at more severe symptoms (severity 6-10).
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59 Demographics and migraine history were similar for the two groups (Table 1). The mean age
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3 for both treatment groups was approximately 41 years, and the median interval between
4
5 migraine attacks was 21 days.

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7 The mean MIS in the patient group taking the attack medication with low symptom severity
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9 was 4.09 ± 1.16 scale units. The mean MIS in the patient group taking the attack medication
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11 with high symptom severity was 8.18 ± 1.41 scale units (Table 2). Comparison of the two
12
13 means showed high statistical significance ($p \leq 0.0001$).
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16 17 18 Efficacy Assessments

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20 Efficacy parameters as a function of frovatriptan threshold score are presented in Table 2.

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22 The initiation of frovatriptan at low symptom severity levels was associated with a more rapid
23
24 achievement of the primary endpoint (time to onset of efficacy) than the initiation of
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26 frovatriptan at high symptom severity levels (42.06 ± 32.33 vs. 49.25 ± 34.92 minutes;
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28 $p=0.0023$; Table 2 and Fig. 1A). Relative frequency distribution of the primary endpoint
29
30 further demonstrated the earlier onset of efficacy in patients who initiated frovatriptan at low
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32 symptom severity levels (median 30 minutes) compared with those who initiated treatment at
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34 high symptom severity levels (median 40 minutes) [Fig. 2A].
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38 The time to complete headache relief was significantly shorter in patients who initiated
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40 frovatriptan at low symptom severity levels compared with patients who initiated treatment at
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42 high symptom severity levels (79.37 ± 65.33 vs. 96.05 ± 100.85 minutes; $p=0.0109$) [Table 2;
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44 Fig. 1B]. Earlier onset of pain relief in patients who initiated treatment at low symptom
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46 severity levels (median 60 minutes) was also seen in a relative frequency distribution of time
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48 to complete headache relief (Fig. 2B).
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51 The endpoint pain free two hours after medication intake did not differ significantly. In the
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53 group of patients with low Migraine Intervention Score (MIS, severity of 1-5), 84.1%
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55 reported being pain free after 2 hours. In the group with high Migraine Intervention Score
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57 (severity 6-10), 83.0% reported being pain free at this point.
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60 The overall frequency of headache recurrence was low (13.5%), and no differences were seen
between patients who initiated frovatriptan at low and high symptom severity levels (11.24%

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3 vs. 13.97%) [Table 2]. Furthermore, the number of frovatriptan tablets needed was non-
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5 significant, but numerically lower for patients who initiated treatment at low symptom
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7 severity levels (1.17 ± 0.42 vs. 1.24 ± 0.56 tablets; $p=0.0575$). However, the need for escape
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9 medication among patients initiating treatment at low symptom severity levels was
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11 significantly less frequent than patients who started treatment at high symptom severity levels
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13 (3.88% vs. 13.73%; $p \leq 0.0001$) [Table 2].
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16 When asked to rate the efficacy of frovatriptan compared with their previous therapy, high
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18 percentages of patients in both groups assessed the onset of efficacy as “good” (81.0% vs.
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20 77.3%), but no significant differences were seen between the two groups (Table 3). Similar
21
22 proportions of patients in both groups also considered the efficacy duration (84.1% vs. 86.8%)
23
24 to be “good” and (compared to previous therapy) response to nausea/vomiting (67.05% vs.
25
26 63.89%) of frovatriptan to be “superior” (Table 3).
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31 Tolerability Assessments

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33 Frovatriptan was generally well tolerated regardless of when the therapy was initiated, and
34
35 more than half the patients in the overall study population (64.4%) rated tolerability of
36
37 frovatriptan as being “superior” compared with their previous therapy. No significant
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39 differences in tolerability assessments were seen between patients who started treatment at
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41 low symptom severity levels and those who started treatment at high symptom severity levels
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43 (Table 3).
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51 Discussion

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54 The present study examined a very large patient group under everyday treatment conditions
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56 and determined that the initiation of treatment with frovatriptan 2.5 mg at a stage of mild
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58 migraine attack symptoms, as operationalized using the MIS scale, led to an earlier reduction
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60 of headache pain than treatment initiated at a time when symptoms were more severe. The

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3 need for escape medication was also significantly reduced by initiating medical intervention
4 with triptans at a stage of mild attack symptom severity. No significant differences were
5 found in the frequency of recurrence headaches, the number of required tablets or tolerability.
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7 This means that no disadvantages were found that might counterbalance the improved
8 efficacy. The frequency of being pain free two hours after medication intake did not differ
9 significantly between the groups. The main clinical advantage of treating mild symptoms
10 therefore lies in an earlier symptom relief within the initial two hours.
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20 The MIS scale allows a patient to identify the optimal time for intervention in an
21 operationalized manner using a method that does not depend on a single symptom such as
22 pain intensity, as is often the case in most clinical studies [9, 12, 13, 18, 19]. In the current
23 study, this strategy accelerated the achievement of efficacy onset and complete headache
24 relief. Simultaneously, the reduced need for escape medication suggests that use of this
25 method can lead to improvements in the cost-effectiveness. Adverse effects were no more
26 likely to occur and the potential for developing medication overuse headache was not
27 increased.
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40 The study was performed in an open-label manner under everyday conditions, and patients
41 were allowed to choose the symptom severity level at which they initiated self-medication.
42 Interestingly, the overwhelming majority of patients (approximately 83%) did not initiate the
43 study medication until symptoms were more severe. This suggested that patients had a
44 tendency to save the medication for use in particularly severe cases, with the hope that the
45 migraine attacks would improve spontaneously, or that the attack would not progress beyond
46 less severe, tolerable symptoms. However, patients who chose to self-medicate at low
47 symptom severity levels achieved efficacy more rapidly. Due to the high prevalence of
48 migraines and the extensive suffering of migraine patients, the decision-making process with
49 regards to the appropriate time and conditions for initiating treatment with a triptan is
50 essential for optimizing the efficacy of these medications [1]. Therefore, patient knowledge at
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3 the time of self-medication contributes a great deal to treatment efficacy under everyday
4 conditions, and extensive consultation should be provided to patients regarding the best time
5 for them to take their medicine [9, 11, 13, 17-19, 21, 23-26, 28-32, 38]. The MIS scale can
6 help overcome this barrier by providing a basis for communication as well as an
7 operationalized method for selecting the time at which treatment is initiated.
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16 Several limitations of this study should be noted. The open-label, single-arm study design
17 may have resulted in potential patient bias, and the lack of a placebo treatment arm did not
18 allow the therapeutic gain of the study treatment to be determined [10]. However, this study
19 design allowed for an analysis of the natural decision-making process of patients to be made.
20
21 The reason for the earlier onset of efficacy remains unclear, and it is not known whether the
22 attacks between the groups were essentially different or if pharmacokinetic parameters are
23 responsible for the differences [13]. The selection of efficacy parameters was another
24 potential limitation of the study. Traditionally, previous studies investigating the efficacy of
25 triptans have instructed patients not to initiate the study medication until the pain intensity is
26 moderate or severe [39]. However, patients in the current study were given permission to
27 choose the time and symptom severity level at which treatment was initiated. As a result, the
28 standard definition of treatment response could not be used in this study – i.e. a responder rate
29 is typically based solely on the symptom of pain intensity and an initial intensity that is
30 moderate or severe. To overcome this issue, the time period between treatment initiation and
31 the achievement of pain reduction or pain relief was reported in the current study, which
32 could be easily measured using a clock.
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53 **The comparison of the study medication with previous medication might be biased, because**
54 **patients satisfied with their current treatment might be less inclined to take part in a study**
55 **involving a different treatment. On the other hand, it would have also been possible that the**
56 **study medication was shown to be equally or less effective than any previous medication.**
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5 Recent randomized, double-blinded, placebo-controlled clinical trials have examined the early
6 use of triptans for therapy of migraine headaches [13, 25, 26, 29, 32, 40-43]. In addition, a
7 number of open-label or un-blinded studies have been published that show the benefits of
8 treatment during the early phases of a migraine attack [9, 11, 19, 20, 22, 28, 32]. The “Act
9 when Mild” study, performed under carefully controlled conditions with a rigorous study
10 design, showed that improved efficacy could be achieved when attacks were treated within
11 the first hour of an attack or when pain intensity was mild [13]. Cady et al. [44] also
12 demonstrated the superior efficacy of early frovatriptan use compared with late frovatriptan
13 use in a double-blind, randomized, placebo-controlled study. Data from the current study
14 support these results and confirms the efficacy of early therapy under everyday conditions,
15 where patients are free to choose the time of treatment initiation. Therefore, using the MIS
16 scale to operationalizing this decision-making process allows patients to analyze this complex
17 situation, which gives them a measureable standard for determining when to initiate
18 treatment.
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38 At the start of a migraine attack, it can often be difficult to decide whether the headache
39 phenotype is indeed that of a migraine or of a tension-type headache. An exact frequency
40 cannot be shown by our study, because symptoms evolve gradually within the first two hours
41 and this development is influenced and overshadowed by effects of the medication. Therefore,
42 no conclusion can be made about the extent to which frovatriptan is also effective for tension-
43 type headaches phenotype.
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53 In recent years, several studies analyzing the expectations of patients in migraine therapy have
54 been performed [45, 47]. The primary expectations include rapid onset of efficacy and pain
55 relief, allowing for rapid return to normal activities [10, 13]. Despite these clear expectations,
56 migraine patients often to wait for taking acute medication, which was confirmed by the
57 results of the present study. Reasons for this include: uncertainty as to whether the headache
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3 pain is actually a migraine attack; a desire to wait and see if pain intensity and symptoms
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5 develop to the point where treatment with a triptan is necessary; worry that early medication
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7 use will lead to tolerance or adverse effects; fear of headache from medication overuse; and
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9 limitation due to budgeting of medication prescriptions.. To counteract these preconceptions
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11 and the resulting delay in self-medication, clear patient education and effective patient-
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13 physician communication are required to ensure effective use of the medication [46, 47]. Use
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15 of the MIS scale can also help to improve physician-patient communication, a key to
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17 individual improvement of efficacy.
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23 In conclusion, the results of this study demonstrate that operationalized intervention with
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25 frovatriptan 2.5 mg using the MIS scale is a valuable method for improving the treatment of
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27 migraine attacks. Furthermore, it seems reasonable to recommend that patients should initiate
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29 self-medication at an early stage of low symptom severity during migraine attacks.
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References

1. Jensen R, Stovner LJ. Epidemiology and comorbidity of headache. *Lancet Neurol* 2008;7:354-61.
2. Olesen J. International Classification of Headache Disorders, Second Edition (ICHD-2): current status and future revisions. *Cephalalgia* 2006;26:1409-10.
3. Olesen J, Leonardi M. The burden of brain diseases in Europe. *Eur J Neurol* 2003;10:471-7.
4. Saunders K, Merikangas K, Low NC, et al. Impact of comorbidity on headache-related disability. *Neurology* 2008;70:538-47.
5. Hawkins K, Wang S, Rupnow M. Direct cost burden among insured US employees with migraine. *Headache* 2008;48:553-63.
6. Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. *Cephalalgia* 2006;26:742-6.
7. Silberstein SD, Olesen J, Bousser MG, et al. The International Classification of Headache Disorders, 2nd Edition (ICHD-II)--revision of criteria for 8.2 Medication-overuse headache. *Cephalalgia* 2005;25:460-5.
8. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders. 2nd ed. *Cephalalgia* 2004;24 Suppl. 1:1-160.
9. Dowson AJ, Mathew NT, Pascual J. Review of clinical trials using early acute intervention with oral triptans for migraine management. *Int J Clin Pract* 2006;60:698-706.
10. Ferrari MD, Roon KI, Lipton RB, Goadsby PJ. Oral triptans (serotonin 5-HT(1B/1D) agonists) in acute migraine treatment: a meta-analysis of 53 trials. *Lancet* 2001;358:1668-75.
11. Pascual J, Cabarrocas X. Within-patient early versus delayed treatment of migraine attacks with almotriptan: the sooner the better. *Headache* 2002;42:28-31.
12. Lampl C, Huber G, Haas S, et al. Difference in triptan effect in patients with migraine and early allodynia. *Cephalalgia*. 2008 Jul;28(10):1031-8.

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13. Goadsby PJ, Zanchin G, Geraud G, et al. Early vs. non-early intervention in acute migraine-'Act when Mild (AwM)'. A double-blind, placebo-controlled trial of almotriptan. *Cephalalgia* 2008;28:383-91.
 14. Silberstein SD, . Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review). Report of the quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2000;55:754-63.
 15. Silberstein SD, Mannix LK, Goldstein J, et al. Multimechanistic (sumatriptan-naproxen) early intervention for the acute treatment of migraine. *Neurology* 2008;71:114-21.
 16. Schoenen J, De Klippel N, Giurgea S, et al. Almotriptan and its combination with aceclofenac for migraine attacks: a study of efficacy and the influence of auto-evaluated brush allodynia. *Cephalalgia* 2008;28:1095-105.
 17. Hu XH, Ng-Mak D, Cady R. Does early migraine treatment shorten time to headache peak and reduce its severity? *Headache* 2008;48:914-20.
 18. Freitag F, Smith T, Mathew N, et al. Effect of early intervention with almotriptan vs placebo on migraine-associated functional disability: results from the AEGIS Trial. *Headache* 2008;48:341-54.
 19. Mathew NT, Finlayson G, Smith TR, et al. Early intervention with almotriptan: results of the AEGIS trial (AXERT Early Migraine Intervention Study). *Headache* 2007;47:189-98.
 20. Gupta VK. Pre-emptive/early intervention with triptans in migraine: hope, hype and hazard. *Int J Clin Pract* 2007;61:350-2.
 21. Charles JA. Early treatment of juvenile migraine reduces disability with disease modification implications. *J Headache Pain* 2007;8:139-40.
 22. Jelinski SE, Becker WJ, Christie SN, et al. Pain free efficacy of sumatriptan in the early treatment of migraine. *Can J Neurol Sci* 2006;33:73-9.
 23. Moschiano F, D'Amico D, Allais G, et al. Early triptan intervention in migraine: an overview. *Neurol Sci* 2005;26 Suppl. 2:s108-10.

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24. Kwong WJ, Taylor FR, Adelman JU. The effect of early intervention with sumatriptan tablets on migraine-associated productivity loss. *J Occup Environ Med* 2005;47:1167-73.
25. Brandes JL, Kudrow D, Cady R, et al. Eletriptan in the early treatment of acute migraine: influence of pain intensity and time of dosing. *Cephalalgia* 2005;25:735-42.
26. Mathew NT, Kailasam J, Meadors L. Early treatment of migraine with rizatriptan: a placebo-controlled study. *Headache* 2004;44:669-73.
27. Lainez M. Clinical benefits of early triptan therapy for migraine. *Cephalalgia* 2004;24 Suppl. 2:24-30.
28. Dowson AJ, Massiou H, Lainez JM, Cabarrocas X. Almotriptan improves response rates when treatment is within 1 hour of migraine onset. *Headache* 2004;44:318-22.
29. Winner P, Mannix LK, Putnam DG, et al. Pain-free results with sumatriptan taken at the first sign of migraine pain: 2 randomized, double-blind, placebo-controlled studies. *Mayo Clin Proc* 2003;78:1214-22.
30. Mathew NT. Early intervention with almotriptan improves sustained pain-free response in acute migraine. *Headache* 2003;43:1075-9.
31. Pascual J. Clinical benefits of early triptan therapy for migraine. *Headache* 2002;42 Suppl. 1:10-7.
32. Cady RK, Sheftell F, Lipton RB, et al. Effect of early intervention with sumatriptan on migraine pain: retrospective analyses of data from three clinical trials. *Clin Ther* 2000;22:1035-48.
33. Lipton RB, Bigal ME, Ashina S, et al. Cutaneous allodynia in the migraine population. *Ann Neurol* 2008;63:148-58.
34. Landy S, Rice K, Lobo B. Central sensitisation and cutaneous allodynia in migraine: implications for treatment. *CNS Drugs* 2004;18:337-42.
35. Markus F, Mikko K. Frovatriptan review. *Expert Opin Pharmacother* 2007;8:3029-33.

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2
3 36. Balbisi EA. Frovatriptan: a review of pharmacology, pharmacokinetics and clinical
4 potential in the treatment of menstrual migraine. *Ther Clin Risk Manag* 2006;2:303-8.
5
6
7 37. Poolsup N, Leelasangaluk V, Jittangtrong J, et al. Efficacy and tolerability of
8 frovatriptan in acute migraine treatment: systematic review of randomized controlled trials. *J*
9
10 *Clin Pharm Ther* 2005;30:521-32.
11
12
13 38. Gobel H, Winter P, Boswell D, et al. Comparison of naratriptan and sumatriptan in
14 recurrence-prone migraine patients. Naratriptan International Recurrence Study Group. *Clin*
15 *Ther* 2000;22:981-9.
16
17
18 39. Edmeads J. Defining response in migraine: which endpoints are important? *Eur*
19 *Neurol* 2005;53 Suppl. 1:22-8.
20
21
22 40. Klapper J, Lucas C, Rosjo O, Charlesworth B. Benefits of treating highly disabled
23 migraine patients with zolmitriptan while pain is mild. *Cephalalgia* 2004;24:918-24.
24
25
26 41. Loder E. Menstrual migraine: timing is everything. *Neurology* 2004;63:202-3.
27
28
29 42. Cady R, Martin V, Mauskop A, et al. Efficacy of Rizatriptan 10 mg administered
30 early in a migraine attack. *Headache* 2006;46:914-24.
31
32
33 43. Martin V, Cady R, Mauskop A, et al. Efficacy of rizatriptan for menstrual migraine in
34 an early intervention model: a prospective subgroup analysis of the rizatriptan TAME (Treat
35 A Migraine Early) studies. *Headache* 2008;48:226-35.
36
37
38 44. Cady R, Elkind A, Goldstein J, Keywood C. Randomized, placebo-controlled
39 comparison of early use of frovatriptan in a migraine attack versus dosing after the headache
40 has become moderate or severe. *Curr Med Res Opin* 2004;20:1465-72.
41
42
43 45. Lipton RB, Hamelsky SW, Dayno JM. What do patients with migraine want from
44 acute migraine treatment? *Headache* 2002;42 Suppl. 1:3-9.
45
46
47 46. Edmeads J. Communication issues in migraine diagnosis. *Can J Neurol Sci* 2002;29
48 Suppl. 2:S8-10.
49
50
51 47. Lanteri-Minet M, Díaz-Insa S, Leone M, Vila C, Clissold SP; START Study. Efficacy of
52 almotriptan in early intervention for treatment of acute migraine in a primary care setting: the
53 START study. *Int J Clin Pract*. 2010 Jun;64(7):936-43.
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Table 1 Demographic data of the treated population

	Triptan Threshold Score	
	MIS 1 - 5	MIS 6 - 10
N	258	1260
Age (years)		
Mean	40.85	41.71
S.D.	12.93	12.81
Median	40.85	41.75
Minimum	17.17	15.18
Maximum	73.56	79.47
Sex, <i>n</i> (%)		
Female	187 (72.5)	1040 (82.5)
Male	71 (27.5)	220 (17.5)
Race, <i>n</i> (%)		
Caucasian/White	258 (100%)	1260 (100%)
Height (cm)		
Mean	170.56	169.59
S.D.	7.64	7.68
Median	170.0	169.0
Minimum	153.0	150.0
Maximum	190.0	200.0
Weight (kg)		
Mean	72.01	69.52
S.D.	12.22	12.05
Median	70.0	68.0
Minimum	45.0	38.0
Maximum	119.0	170.0
Attack interval (days)		
Mean	24.3	26.6
S.D.	16.73	22.93
Median	21.0	21.0
Minimum	1	1
Maximum	99	240

MIS = Migraine Intervention Score.

Table 2 Efficacy parameters as a function of triptan threshold score

	MIS Values		p-value
	1 - 5	6 - 10	
N	258	1260	
MIS values (units)			
Mean	4.09	8.18	p < 0.0001
S.D.	1.16	1.41	
Median	5.00	8.00	
Minimum	1.00	6.00	
Maximum	5.00	10.00	
Time to onset of efficacy (minutes)			
Mean	42.06	49.25	p = 0.0023
S.D.	32.33	34.92	
Median	30.00	40.00	
Minimum	1.00	5.00	
Maximum	240.00	300.00	
Time to pain-free (minutes)			
Mean	79.37	96.05	p = 0.0109
S.D.	65.33	100.85	
Median	60.00	70.00	
Minimum	10.00	15.00	
Maximum	530.00	1600.00	
Headache recurrence [<i>n</i> (%)]			
no	224 (86.82)	1053 (83.57)	p = 0.2711
yes	29 (11.24)	176 (13.97)	
missing	5 (1.94)	31 (2.46)	
Tablets needed [<i>n</i> (%)]			
Mean	1.17	1.24	p = 0.0575
S.D.	0.42	0.56	
Median	1.00	1.00	
Minimum	1.00	1.00	
Maximum	4.00	6.00	
Escape medication needed [<i>n</i> (%)]			
yes	10 (3.88)	173 (13.73)	p < 0.0001
no	248 (96.12)	1087 (86.27)	

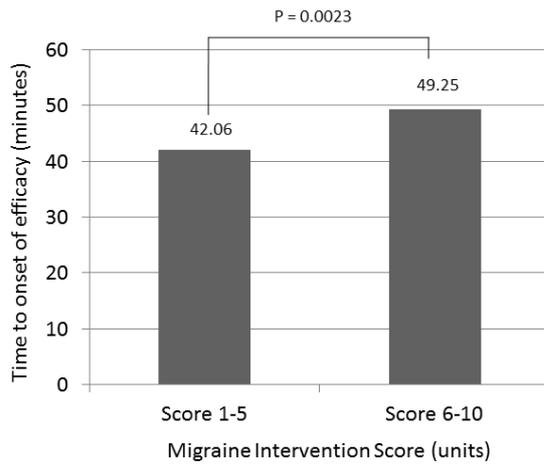
MIS = Migraine Intervention Score.

Table 3 Evaluation of the therapy by patients (*compared to previous therapy)

	Migraine Intervention Score Values		p-value
	1 – 5	6 - 10	
Efficacy onset [<i>n</i> (%)]			
Good	209 (81.01)	974 (77.30)	p = 0.4114
Moderate	43 (16.67)	246 (19.52)	
Bad	5 (1.94)	34 (2.70)	
Missing	1 (0.39)	6 (0.48)	
Efficacy duration [<i>n</i> (%)]			
good	217 (84.11)	1094 (86.83)	p = 0.2649
moderate	36 (13.95)	134 (10.63)	
bad	4 (1.55)	27 (2.14)	
missing	1 (0.39)	5 (0.40)	
Response Nausea/Vomiting* [<i>n</i> (%)]			
superior	165 (63.95)	813 (64.52)	p = 0.2364
equal	80 (31.01)	397 (31.51)	
Inferior	2 (0.78)	32 (2.54)	
missing	11 (4.26)	18 (1.43)	
Tolerability* [<i>n</i> (%)]			
superior	173 (67.05)	805 (63.89)	p = 0.4043
equal	82 (31.78)	437 (34.68)	
inferior	1 (0.39)	11 (0.87)	
missing	2 (0.78)	7 (0.56)	

Fig. 1. Time to onset of efficacy (A) and time to pain free (B) as a function of initial symptom development with intake of frovatriptan 2.5mg. The time to achievement of headache response (A) and complete pain relief (B) were both significantly shorter in patients who initiated treatment at Migraine Intervention Scores of 1–5 compared with patients who initiated treatment after reaching scores of 6–10.

A)



B)

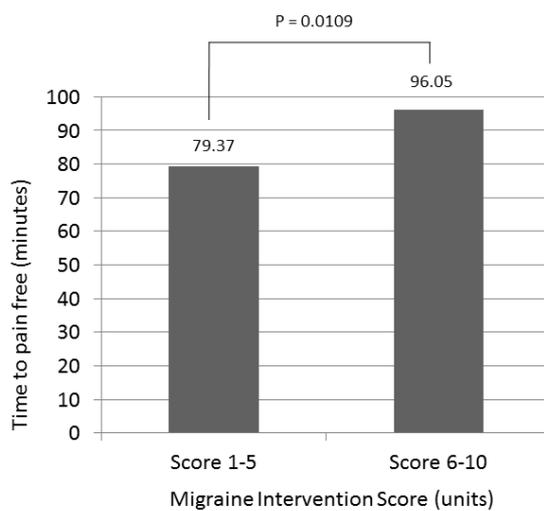
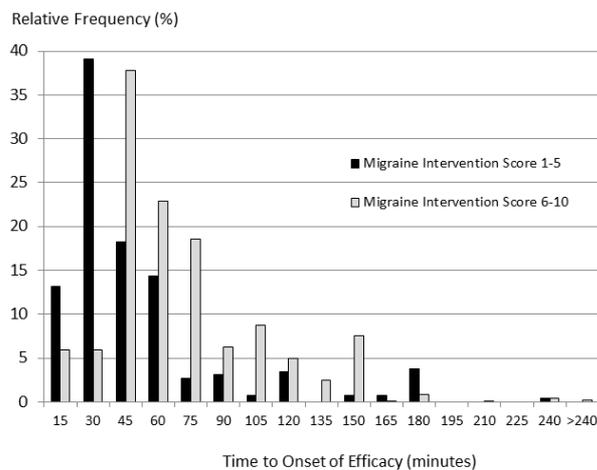
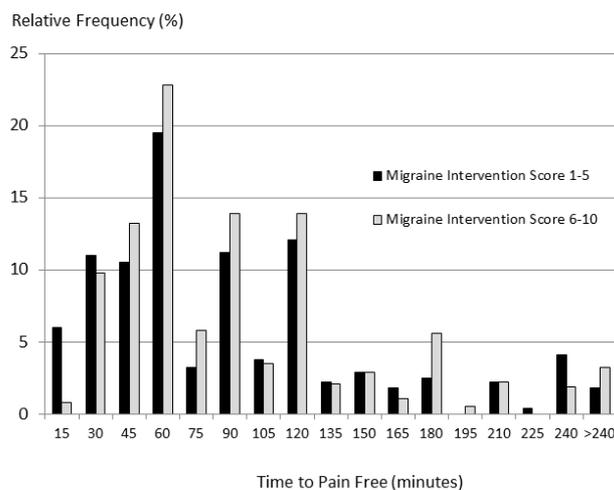


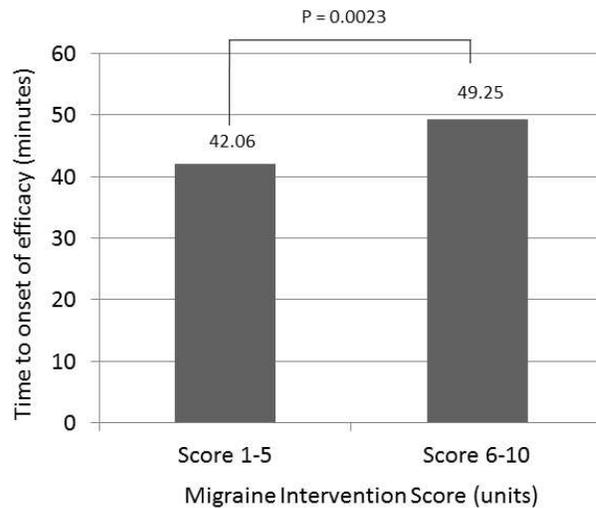
Fig. 2. The relative frequency distribution of the time to onset of efficacy (A) and the time to complete pain relief (B) in patients with a low Migraine Intervention Score (MIS; severity of 1-5) and a high MIS (severity 6-10). A) The onset of efficacy occurred earlier in patients with a low MIS (median 30 minutes) than in patients with a high MIS (median 40 minutes). B) Likewise, earlier onset of complete pain relief was seen in patients with a low MIS (median 60 vs. 70 minutes).

A)

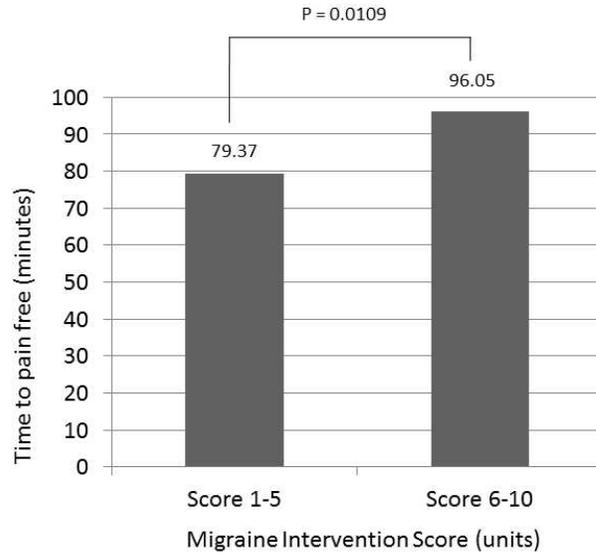


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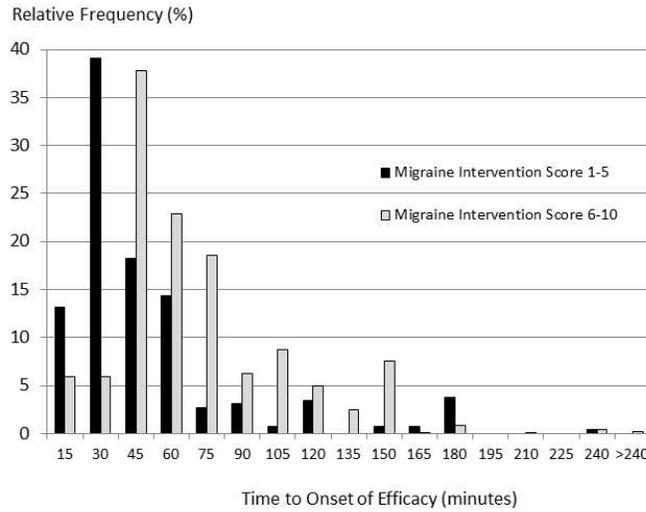


Time to onset of efficacy (A) and time to pain free (B) as a function of initial symptom development with intake of frovatriptan 2.5mg. The time to achievement of headache response (A) and complete pain relief (B) were both significantly shorter in patients who initiated treatment at Migraine Intervention Scores of 1-5 compared with patients who initiated treatment after reaching scores of 6-10.

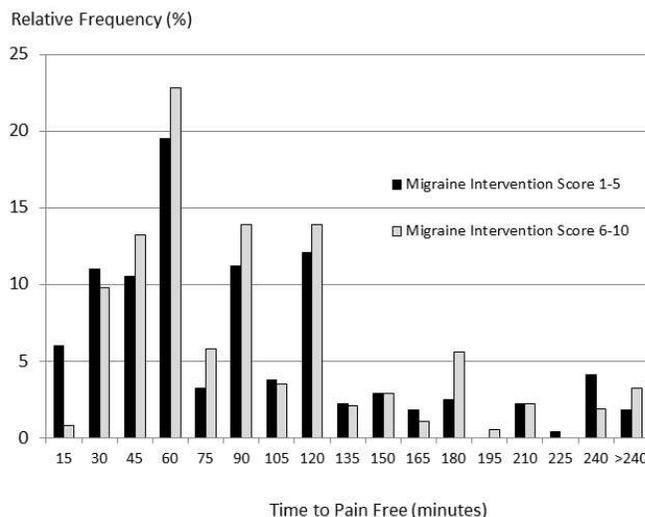


Time to onset of efficacy (A) and time to pain free (B) as a function of initial symptom development with intake of frovatriptan 2.5mg. The time to achievement of headache response (A) and complete pain relief (B) were both significantly shorter in patients who initiated treatment at Migraine Intervention Scores of 1–5 compared with patients who initiated treatment after reaching scores of 6–10.

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The relative frequency distribution of the time to onset of efficacy (A) and the time to complete pain relief (B) in patients with a low Migraine Intervention Score (MIS; severity of 1-5) and a high MIS (severity 6-10). A) The onset of efficacy occurred earlier in patients with a low MIS (median 30 minutes) than in patients with a high MIS (median 40 minutes). B) Likewise, earlier onset of complete pain relief was seen in patients with a low MIS (median 60 vs. 70 minutes).



The relative frequency distribution of the time to onset of efficacy (A) and the time to complete pain relief (B) in patients with a low Migraine Intervention Score (MIS; severity of 1-5) and a high MIS (severity 6-10). A) The onset of efficacy occurred earlier in patients with a low MIS (median 30 minutes) than in patients with a high MIS (median 40 minutes). B) Likewise, earlier onset of complete pain relief was seen in patients with a low MIS (median 60 vs. 70 minutes).