Acta neurol. belg., 2007, **107**, 40-46

Is the Migraid® device an asset in the non-pharmacologic treatment of migraine ?

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Abstract

Non-pharmacologic treatment of migraine attacks is advised by guidelines to be considered. Some patients use digital massage of the temporal arteries. The Migraid® device exerts a constant pressure on the temporal arteries and may be an alternative for the tiring digital massage. The present study investigates whether the new Migraid® device may improve migraine symptoms. In a randomised multi-centre cross-over study the efficacy, safety and tolerability of a 1-hour use of the Migraid® device at the start of the aura is compared with no-device in the treatment of migraine attacks with typical aura. Of the 134 patients who entered the study, 98 were suitable for the intention-to-treat analysis and 83 patients completed the study. Data on 94 Migraid® treated and 87 non-treated attacks have been analysed. Twelve percent of patients (10/83) were pain-free at 2 hours in the Migraid® group versus 1.6% (1/64) in the non-treated group (p = 0.02). After 24-hours 9.6% of patients were pain-free with the Migraid® versus 0% with no treatment. After 2 hours 31.3 % of patients perceived the migraine headache as severe using the Migraid® versus 53.1 % with no treatment. For nausea this was 6.1 % and 15.6 %, respectively (p = 0.01). The device was well tolerated.

In conclusion, 1-hour use of the Migraid® device at the start of the aura improved headache and other migraine symptoms compared to no treatment. Future research with a more appropriate control should determine whether the Migraid® effects are going beyond unspecific placebo effects.

Key words : Acute migraine ; medical device ; Migraid® ; non-pharmacologic treatment.

Introduction

Migraine is a common, multi-factorial neurovascular disorder, typically presented as recurrent disabling attacks of moderate to severe headache, nausea, vomiting, photophobia and phonophobia, and in up to one third of the patients, neurological aura symptoms (Goadsby *et al.*, 2002). Migraine is accompanied by an altered arterial function (Vanmolkot *et al.*, 2007). In the United States and Western Europe, the one-year prevalence of migraine is 11 percent overall : 6 percent among men and 15 to 18 percent among women (Goadsby *et al*., 2002). The significant impact of migraine (i.e., pain, disability, social functioning, quality of relationships, emotional well being and general health) puts a huge burden on the patient, health services and society (Solomon and Price, 1997 ; Hu *et al*., 1999). NSAIDS and triptans are the drugs of choice for acute migraine attacks (Evers *et al.*, 2006). But these medicines are lacking effect in a number of patients (Evers *et al.*, 2006 ; Lohmann and Van der Kuy-de Ree, 2005). The highest absolute pain free percentage at 2 hours is with triptans only about 40% (Ferrari *et al*., 2001). Moreover, triptans are contraindicated in some groups of patients like those with cerebrovascular disease, uncontrolled hypertension, or ischemic heart disease (Goadsby, 1999). In these patients non-pharmacologic treatment may be of particular interest. In addition, many migraine patients try several non-pharmacologic treatments to manage their headache before starting any drug therapy or use non-pharmacologic treatments concurrently with drug therapy (Silberstein, 2000). One of these is digital massage of the temporal arteries. The Migraid® is a new medical device that looks like a stylized headphone exerting a constant pressure of 4 Newton on the temporal arteries just before the ears and may be an alternative for the tiring digital massage.

The objective of the study was to investigate whether the Migraid® device was able to prevent headache or to induce pain relief and/or relief of migraine associated symptoms in patients with migraine with typical aura. Also the safety and tolerability of the device were evaluated.

Patients and methods

STUDY DESIGN

The study was an open randomized cross-over study comparing the device with no treatment. Due

to the shape of the device and the common temporal localization of the migraine headache a fully blinded sham control can hardly be obtained. Therefore, in this first study no treatment was used as the open control. The primary efficacy variable was defined as the proportion of patients without headache two hours after the start of the aura without using rescue-medication. Secondary aims were the proportion of pain-free patients 24 hours after the start of the aura, and the reduction in severity of headache, migraine associated symptoms and use of rescue medication. The study has been approved by the Ethics Committee. Written informed consent has been obtained from all patients.

Patients

Patients up to 65 years old, with a current history of migraine with typical aura according to IHS migraine criteria (Olesen, 2004), and with at least 1 moderate (grade 2) or severe (grade 3) migraine attack per month for at least two months were recruited from 24 general practice centers in the Netherlands. Moderate migraine attacks were defined as attacks that inhibit, but do not fully prevent usual activities ; severe attacks were attacks that prevent all activities (Olesen, 2004). Additionally, the patients enrolled had to be able to distinguish migraine headaches from other headache types (e.g. tension-type headaches) at the onset of a migraine attack. Prophylactic treatment for migraine was allowed during the study provided the dose was kept unchanged. Major exclusion criteria to ensure the safety of the patients during the study were cardio- and cerebrovascular disease and tension-type headache more than 15 days per month. A migraine attack could not be accepted for evaluation if the patient used a painkilling drug within 24 hours before the onset of the attack.

Methods

The patients were instructed in detail to place the Migraid® accurately on the indentation just in front of the ear above the cheekbone in order to exert pressure on both the superficial temporal arteries and to use the Migraid® immediately from the start of their aura symptoms for a total duration of 60 minutes. In both the Migraid® and the non treatment study periods, the patients were instructed not to use rescue medication during the first 2 hours after the start of the aura and were asked to complete diary cards recording details for each of the two migraine attacks including associated symptoms.

Statistical analysis

Based on earlier pilot studies (Heath *et al*., 2004) it was presumed that the Migraid® was effective in 50% of the migraine attacks and in 25% of the non-treated attacks. A sample size of 73 patients (Pocock, 1983) was needed to detect a difference of 25% with a significance level of 5% and a power of 90%. The main analysis population is the intent-to-treat population defined as all randomized patients with data of at least one migraine attack and at least one efficacy assessment. The per protocol population was defined as all randomized patients without any major protocol violation. The effect on migraine symptoms of the Migraid® treatment versus no treatment was compared using the Chi-square test and the Fisher Exact test when the number of patients was too small. These data were also tested for carry-over effects. Data are presented as mean. All comparative tests were performed two-sided with a significance level of 5%. P-values of multiple comparisons were corrected according to Bonferroni. In case rescue medication was used all data on efficacy parameters following the time point at which rescue medication was taken were excluded from the analysis (observed case approach) or, if more appropriate, all data on efficacy parameters following the time point at which rescue medication was taken were replaced with the last available value before the use of rescue medication (Last Observation Carried Forward approach, LOCF). The difference in headache severity between an attack with and without the Migraid® was computed at each time point using the LOCF approach and statistically tested for significance using the Wilcoxon Signed Rank test.

Results

Data presented are data from the intention-to-treat analysis. Figure 1 shows the flow of the study population. Eighty three patients completed the study. Nine of them were excluded from per protocol analysis because of major protocol deviations : two patients were over 65 years of age at the time of study entry and 7 patients reported the use of painkillers within 24 hours before the attack. Three of the 47 patients were withdrawn from the study after the use of the Migraid® device in the first study period : one patient because of lost to follow-up and two patients because they did not record the data on their attack in the diary. Data on 94 Migraid® treated attacks and 87 non treated migraine attacks were recorded. Patient characteristics are presented in Table 1. The large majority of patients were women.

The effect of the Migraid® treatment and non-treatment on the proportion of pain-free attacks 2 hours after the start of the aura, the primary efficacy parameter, is shown in Table 2. The majority of the attacks (n = 136, 92.5%) were not pain-free after two hours. However, the proportion of pain-free attacks was significantly higher using the Migraid® than with no treatment. Using the LOCF

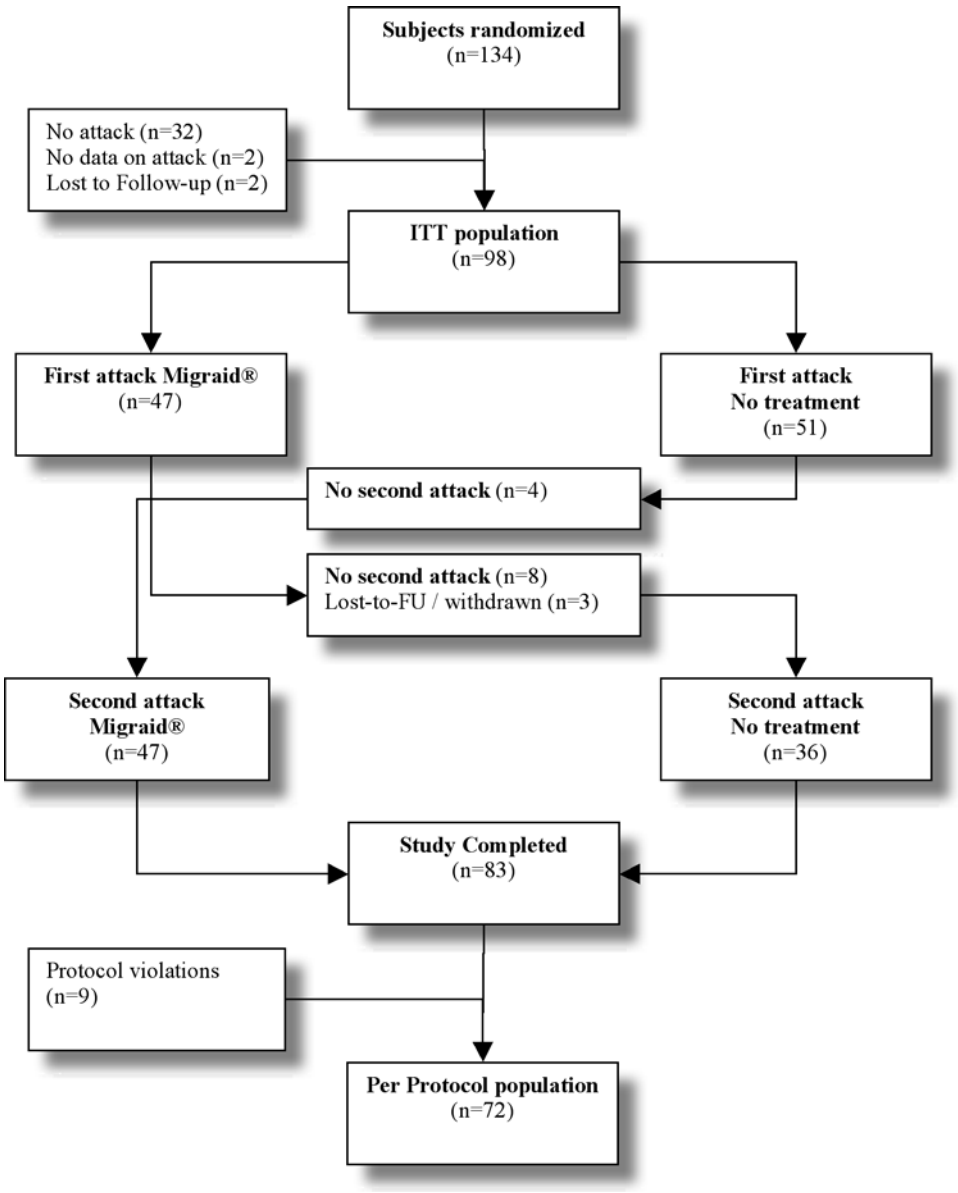

FIG. 1. — Flow diagram of study population.
ITT = intention to treat ; FU = follow-up ; No attack means no second attack occurred within the next 12 weeks.

Table 1

Patient characteristics and migraine history data at baseline of the ITT population (n = 98)

Item		Mean ± SD (range) or number (%)
Age (years)	Male	43.6 ± 10.7 (28, 65)
	Female	47.7 ± 10.4 (24, 74)
Male/female		17/81 (17.3/82.7 %)
Duration of Migraine History (years)		18.7 ± 14.1 (0.2, 59.0)
Number of Moderate Attacks (Last 2 months)		3.4 ± 2.9 (0, 16)
Number of Severe Attacks (Last 2 months)		2.1 ± 2.2 (0, 10)

approach 98.8% of the patients experienced headache after two hours when the Migraid® was not used, with the use of the Migraid®, 89.3% of the patients had headache. Eight of 83 patients (9.6%) who completed the study remained pain-free for 24 hours after the start of the aura using the device versus none after no treatment.

For patients using rescue medication, all data on efficacy following the intake of rescue-medication have been deleted from the analysis (observed case approach). The number of patients using rescue medication increased with time in both groups (Table 3). But the proportion of patients using rescue medication for the attack was 2 hours after start of the aura higher in the non treatment group than in the Migraid® treated group. The same holds for 24 hours after the start of the aura.

Table 2

Primary efficacy parameter : Proportion of Pain-Free Attacks after 120 minutes

Migraid® used ?	Headache (OCA)		P-value no versus yes	
	N	%	OCA	LOCF
No (n = 64)	1	1.6		
Yes (n = 83)	10	12.0	0.0236	0.0102

p-value from Fisher's Exact ; OCA : Observed Case Approach ; LOCF :Last Observed Carried Forward.

Table 3

Use of Rescue Medication

Migraid® Used ?	Time point							
	Start Aura		After 30 minutes		After 2 hours		After 24 hours	
	N	%	N	%	N	%	N	%
No (n = 87)	0	0	6	6.9	21	24.1	62	71.3
Yes (n = 94)	0	0	1	1.1	10	10.6	47	50.0
Bonferroni corrected p-value (NS : not significant)			NS		NS		P = 0.024	

The percentage of patients with severe headache without use of rescue medication is shown in Figure 2. Figure 2a shows the proportion of patients using the 'observed case' approach. In this approach the percentage is calculated from the number of patients with severe headache without use of rescue medication (N), which is decreasing over time. Figure 2b shows the proportion of patients using the 'last observation carried forward' approach. In this approach the percentage is calculated from the number of patients with severe headache without use of rescue medication and patients who took rescue medication for severe headache (N). This number is quite stable and this calculation better reflects the change in severity of headache over time. In both groups, the number of patients experiencing headache rapidly increased after the start of the aura. At 2 hours after start of the aura the proportion of patients experiencing severe headache was 41% lower using the device (30%) versus no treatment (51%). Migraid® treated attacks were not only less severe but also tended to be shorter compared to non-treated attacks (Fig. 2). The difference in severity scores (none, mild, moderate or severe headache) between the two treatments was also calculated, At the start of the aura the attacks tended to be more painful with the Migraid® + 0.19 ± 0.86 on a 4-point scale ($p = 0.39$, Bonferroni corrected). The severity of headache did not differ between treatments after 0.5 and 1 hour, but was less severe from 1.5 up to 24 hours during the Migraid® treated attacks ($p < 0.002$, Bonferroni corrected) (Fig. 3).

As shown in Figure 4, the percentage of patients with nausea at the start of the aura is higher in the Migraid® treated patients. The proportion of patients reporting nausea was less in the Migraid® treated patients as compared with the non-treated patients (at 3 hours : $p < 0.015$, Bonferroni corrected). After 24 hours, the difference was no longer statistically significant. Photo- and/or phonophobia were frequent symptoms in both study groups. At the start of the aura, it was present in more than 70% of the patients (71.3% of the non-treated attacks, versus 72.3% of the treated attacks). In the non-treated attacks, the percentage of patients reporting hypersensibility to light or noise increased after the start of the aura, whereas in the Migraid® treated patients, a decrease was observed. The difference between the two treatments was significant at 1, 1.5, 2, 2.5, and 3 hours after the start of the aura ($p < 0.05$, Bonferroni corrected).

Discussion

The present study demonstrated that the Migraid® device can prevent or decrease headache and other migraine related symptoms in a limited number of patients compared to no treatment.

Due to the lack of an appropriate blinded sham control the present study could not exclude non-specific or placebo effects. A recent meta-analysis of 98 drug studies in acute migraine indicated that 8.8 % of patients were pain-free after 2 hours with placebo (Macedo *et al.*, 2006). In the present study the difference between Migraid® treated and non-treated patients being pain-free 2 hours after the start of the aura was 10.4%, which is very close to 8.8% average placebo response. This strongly

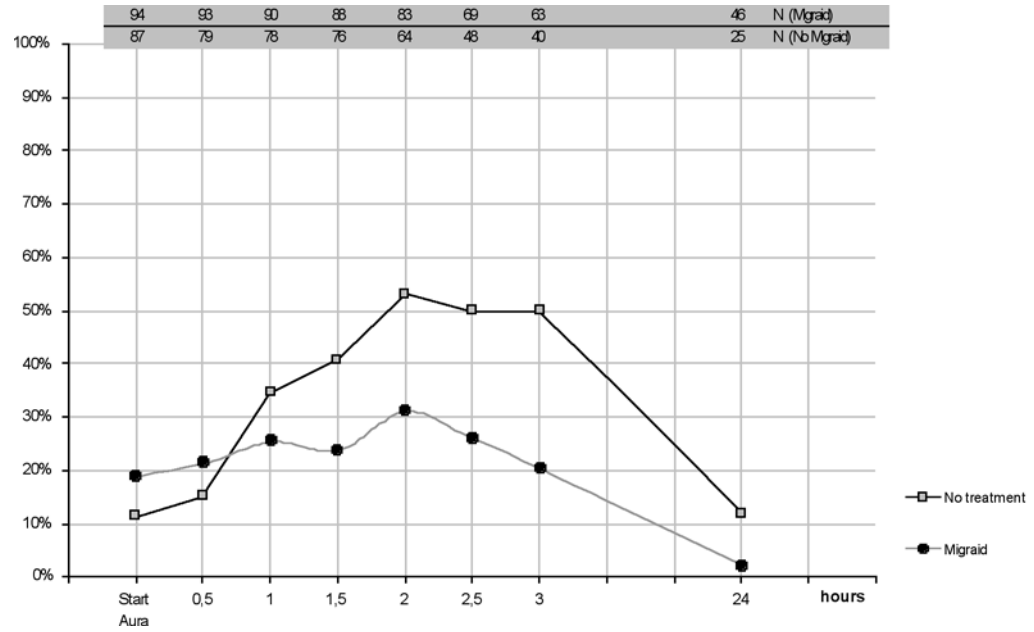

FIG. 2a. — Percentage of patients with severe headache. Observed case approach.
X-axis : time after start aura ; Y-axis : Percentage of patients with severe headache ; N : number of patients for percentage calculation.

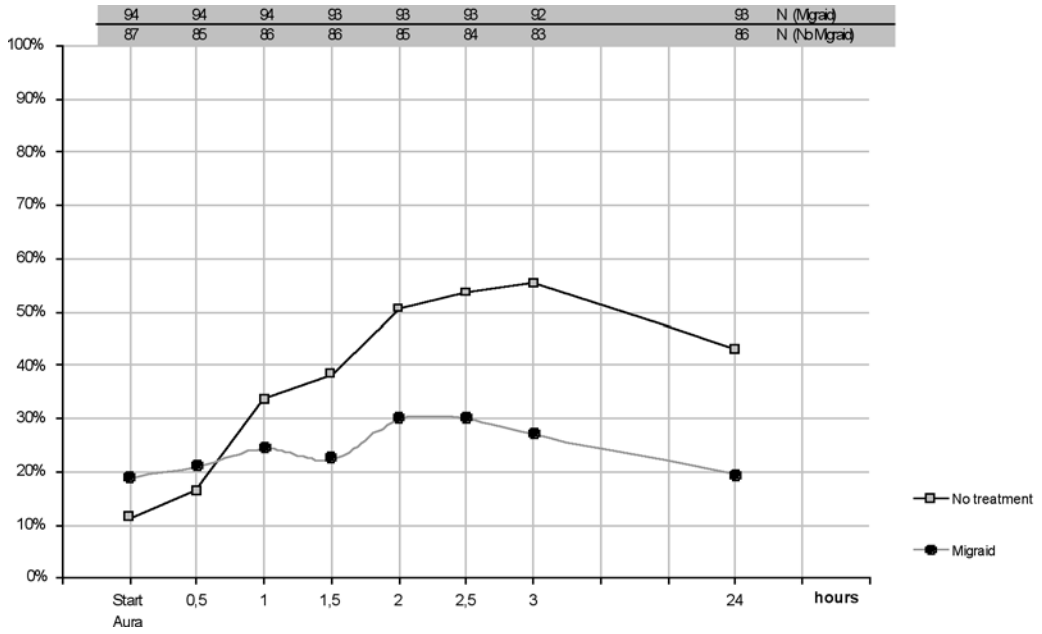

FIG. 2b. — Percentage of patients with severe headache. Last observation carried forward approach.
X-axis : time after start aura ; Y-axis : Percentage of patients with severe headache ; N : number of patients for percentage calculation.

suggests that the large majority of the Migraid® effect – if not all – is due to nonspecific effects. Even larger, up to 30% (Ferrari *et al.*, 2001), nonspecific effects of migraine treatment have been reported with triptans. The nonspecific effects are caused by numerous factors like the patients' and physicians' expectations, the reputation of the treatment, the physicians' attention and the concern in a healing setting (Turner *et al.*, 1994).

To evaluate whether the Migraid® has some specific anti-migraine effects, an appropriate blinded sham control is needed. Due to the shape of the device and the common temporal localization of migraine headache, placing the Migraid® in another way on the head than it is intended to, will decrease the credibility of that position. If one treatment is more credible than the other, this may bias the study results (Turner *et al.*, 1994). To the

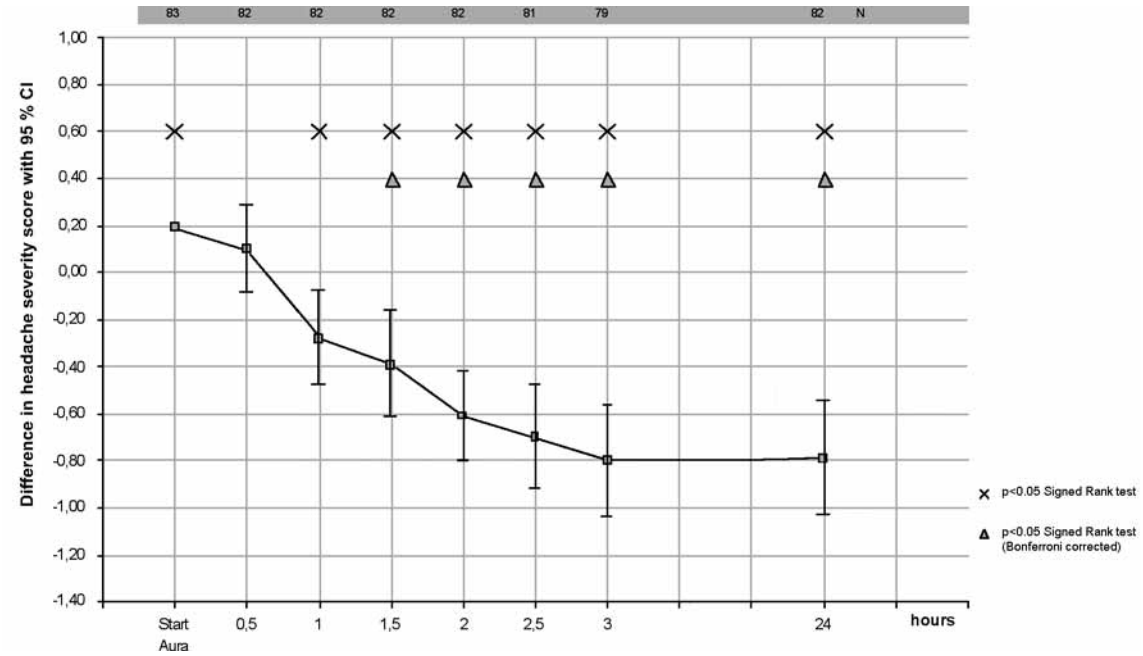

FIG. 3. — Difference in headache severity between treatment with and without the use of the Migraid® using the last observation forward approach. A positive value represents a more severe headache with the Migraid® than without ; X-axis : time after start of aura ; Y-axis : Mean difference in headache severity with 95% confidence intervals.

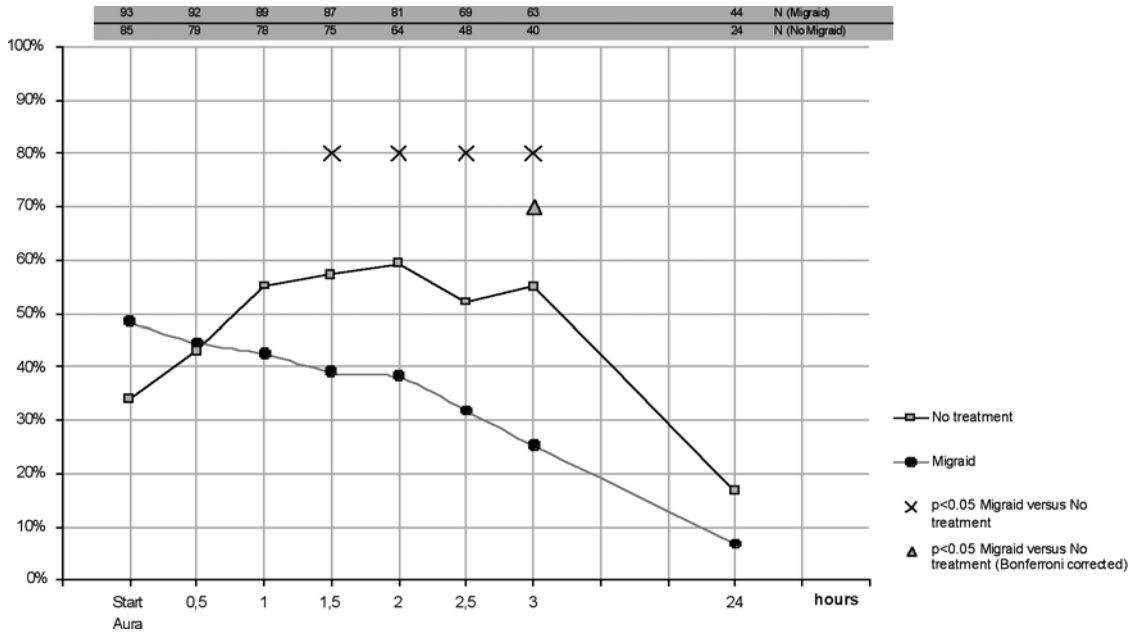

FIG. 4. — Percentage of patients with nausea. Observed case approach.
X-axis : time after start aura ; Y-axis : Percentage of patients with nausea ; N : number of patients for percentage calculation.

extent that the patient or clinician believes a treatment may be ineffective, the power of nonspecific, placebo effects will be reduced or underestimated. The assessment of non-pharmacologic therapies in general is hampered in the management of migraine because the use of a blinded control to reduce bias is difficult in clinical studies with medical devices (Pryse-Philips *et al.*, 1998). Also the Food and Drug Administration reported that medical device evaluation has demonstrated often difficult or impossible to mask the patient or investigator because a placebo or convincing sham treatment may not be feasible. In the case of the Migraid® device, a study with placebo tablets and triptans, rather than an incorrect placement of the Migraid® on the head, may further determine the specific effects of the Migraid® device.

Another limitation of the present study could have been the fact that up to 20% of patients did already have headache at the start of the aura which

may suggest that these patients applied the device too late. If so, it cannot be excluded that the effect of the device might be larger than in the present study, if the device is applied correctly : immediately at the start of the aura. However, it is known that aura symptoms do not always precede headache in a migraine attack. In a large study on aura timing, aura occurred *during* the headache in 18.7% (Kelman, 2004).

The American Academy of Neurology guidelines regarding migraine treatment recommend to consider non-pharmacologic therapies and also to take patient preference into consideration (Silberstein, 2000). The behavioral therapies are classified into relaxation training, biofeedback therapy, and cognitive-behavioral training also called stress-management training. The physical treatments include acupuncture, cervical manipulation, and mobilization therapy. The non-pharmacologic treatment could be suitable for those migraine patients that prefer these interventions over drug treatment. In addition, these non-pharmacologic therapies can be of help in migraine patients that lack effect from triptans or NSAIDs, poorly tolerated drug treatment or have definite contraindications for NSAIDs or triptans, like patients with important cardiovascular diseases. Other groups of patients with a contraindication for triptans are pregnant patients, patients planning to become pregnant or nursing patients. Finally, a last group eligible for non-pharmacologic treatment are the patients with a history of long-term, frequent or excessive use of analgesics or acute medications that can aggravate headache problems (Paemeleire *et al.*, 2006) or lead to decreased responsiveness to other pharmacotherapy.

In conclusion, 1-hour use of the Migraid® device at the start of the aura improved headache and other migraine symptoms. These anti-migraine effects of the Migraid® were very close to the effects reported from placebo. Future research with a more appropriate control should investigate whether the Migraid® effects are going beyond unspecific placebo effects.

Acknowledgements

The authors thank the company Koopman International B.V. for their financial support and the statistician, Henriët Nienhuis of Nienhuis MediStat for her thorough and accurate statistical input. The authors also thank the 24 general practitioners from the Dutch Association for Physicians active in Medical Scientific Research (AMWO) who participated in this study.

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