Research Article

CLINICAL INVESTIGATION

HERBAMIG in the prevention of migraine headaches: results of a study based on real-life data

Abstract

Background: Migraine is a widespread neurological disorder, affecting approximately 12% of the global population, with significant socioeconomic and personal impacts. The underdiagnosis and undertreatment of migraines exacerbate the burden, highlighting the need for effective preventive treatments. Dietary supplements, such as Tanacetum parthenium (feverfew), Salix alba (willow bark), vitamins B2 and B12, and coenzyme Q10, have shown potential benefits in migraine prevention.

Objective: This study aimed to evaluate the efficacy and safety of HERBAMIG, a dietary supplement combining these ingredients, in preventing migraine headaches.

Methods: A 3 month observational clinical follow-up was conducted in France, involving 302 participants diagnosed with episodic migraine. Patients took one capsule of HERBAMIG daily, containing 90 mg of feverfew, 150 mg of willow bark, 40 mg of coenzyme Q10, 15 mg of riboflavin, and 0.1 mg of cyanocobalamin. Primary endpoint was the change in the number of migraine days per month. Secondary endpoints included changes in migraine intensity, duration, Headache Impact Test (HIT-6), and Migraine Disability Assessment Scale (MIDAS) scores.

Results: Out of 302 enrolled patients, 256 completed the study. HERBAMIG significantly reduced the number of migraine days by 28.4% (from 8.1 ± 2.5 to 5.8 ± 2.4 days per month, $p<0.001$). Migraine intensity decreased by 2.1 points on a 10-point scale (from 7.8 ± 1.4 to 5.7 ± 1.8, $p<0.001$), and duration reduced by 2.2 hours (from 17.3 ± 7.0 to 15.1 ± 6.9 hours, $p<0.001$). Significant improvements were observed in HIT-6 (decrease of 4.8 ± 0.6 points, $p<0.001$) and MIDAS scores (decrease of 5.2 ± 0.4 points, $p<0.001$). Adverse events were mild and transient, with no serious side effects reported.

Conclusion: HERBAMIG, a combination of feverfew, willow bark, riboflavin, cyanocobalamin, and coenzyme Q10, effectively reduces the frequency, intensity, and duration of migraines, significantly improving patients' quality of life. Further research is warranted to confirm these findings and elucidate the mechanisms of action.

Keywords: Migraine prevention • HERBAMIG • Dietary supplement • Tanacetum parthenium • Salix alba • Riboflavin • Cyanocobalamin • Coenzyme Q10 • Headache impact • Clinical study • Quality of life

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Introduction

Migraine is a prevalent neurological disorder characterized by recurrent, disabling headaches that can significantly impact an individual's quality of life. It affects approximately 12% of the general population, with a higher incidence in women between the onset of menstruation and menopause [1]. Migraines are often accompanied by additional symptoms such as nausea, vomiting, and sensory disturbances, further contributing to the burden of the condition [2].

Socioeconomic impact of migraines

The socioeconomic impact of migraines is substantial, with direct and indirect costs posing a significant burden on both individuals and healthcare systems [3]. Migraineurs often experience impaired quality of life and reduced productivity, leading to missed work days and decreased earning potential [4]. Additionally, the underdiagnosis and undertreatment of migraines further exacerbate the economic and personal toll of the condition [4].

Recent research on the burden of migraines

Recent studies have aimed to characterize the current burden of migraines in various regions, including Canada and the United States [5]. These studies have highlighted the continued high prevalence of migraines, the significant impact on quality of life, and the substantial direct and indirect costs associated with the condition. The Canadian study, for example, found that patients with migraines who had failed at least two prior prophylactic therapies incurred significant direct medical costs and experienced a substantial reduction in quality of life [5].

Potential role of dietary supplements in migraine prevention

Given the significant burden of migraines, the exploration of new and effective treatment options is crucial. Dietary supplements have been investigated as a potential approach to migraine prevention, with some studies suggesting potential benefits [6]. However, the efficacy and safety of these supplements in the prevention of migraines have not been fully elucidated, and further research is needed to understand their role in the management of this condition.

Tanacetum parthenium, also known as feverfew, is a herbal supplement that has been studied for its potential in reducing the frequency and severity of migraines [6]. In an open prospective study, its combination with the Salix alba plant showed beneficial effects on the duration and intensity of migraine attacks [7].

Thesis work has also shown that parthenolide, the main active ingredient in feverfew, acts as a modulator of Transient Receptor Potential Ankyrin 1 (TRPA1) and Transient Receptor Potential Vanilloid-1 (TRPV1) receptors involved in pain transmission, and is strongly present in the trigeminal system and meninges [8].

A more recent study demonstrated the efficacy of a combination of the two plants, administered orally at 150 mg of extracts per day, in preventing migraine attacks. Specific migraine evaluation scores such as HIT-6 and MIDAS showed significant results from the second month of treatment. Patients' quality of life also improved significantly [9].

Riboflavine and cyanocobalamin (vitamin B2 and B12) have also been investigated for their potential in migraine prevention, with some studies suggesting positive effects on migraine frequency and severity [10,11]. Also coenzyme Q10 has shown promising results, potentially through its antioxidant and mitochondrial function-supporting properties [12].

Taking into account the scientific literature, a new formula called HERBAMIG was proposed based on Tanacetum parthenium, Salix alba, vitamins B12 and B2 and coenzyme Q10. The aim was to determine whether the synergistic activity of all these ingredients would be effective in preventing migraine.

Materials and Methods

This is a 3 months observational clinical follow-up, performed in France between January and May 2021. The study was conducted in a context of routine practice. The trial complied with the International Conference on Harmonisation Guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and relevant national and local regulations. At the time of screening, participants signed consent forms. Data were anonymized before analysis. The trial sponsor, NATURVEDA SAS, provided the trial medication and performed the data analysis.

Trial medication

HERBAMIG is a dietary supplement registered in France. It is available in capsule form, with a dosage of one capsule per day. Each capsule contains the following components: 90 mg of feverfew (*Tanacetum parthenium*) standardized to 0.1% parthenolide, 150 mg of Salix alba standardized to 20% salicin, 40 mg of coenzyme Q10, 15 mg of riboflavin (1072% of the Nutrient Reference Values, NRVs), and 0.1 mg of cyanocobalamin (400% of NRVs). Rice flour and magnesium stearate are included as fillers and stabilizers.

Inclusion criteria

Patients eligible for this study were required to meet the following criteria: They had to be between 18 and 55 years old, male or female, and diagnosed with migraine with or without aura according to the International Classification of Headache Disorders, 3rd edition (ICHD-3: 1.1). Additionally, they must have been diagnosed with migraines for more than one year, experienced at least five migraine days per

month, and had each migraine attack lasting at least four hours

Exclusion criteria

Patients were excluded from the study if they had used a new treatment for migraines within six months prior to the study, were diagnosed with medication overuse headaches, had allergies to salicylates or hypersensitivity to the study medication, or had a history of drug abuse or dependency. Other exclusion criteria included chronic psychiatric or systemic diseases, being pregnant or breastfeeding, and use of neuroleptics, anxiolytics, or new prophylactic treatment for migraines within three months before the start of the study. Study participants were asked to maintain their usual treatments, so that the only variation was the use of HERBAMIG.

Trial end points

The primary evaluation criterion was the number of migraine days after 3 month of treatment (T3). A migraine day was defined as any day on which the patient had a migraine or probable migraine. Defined as a calendar day in which headache pain lasted, at least, 4 consecutive hours and met criteria for migraine or probable migraine (subtype in which only one migraine criterion is absent), or a day in which acute migraine specific medication was used to treat a headache of any duration.

Secondary endpoints were pain intensity ratings on an analog scale of 0 to 10, where 0 is no pain and 10 is intolerable pain. Then the evaluation of the duration of migraines in hours was analyzed. This is defined by the duration of the headache and the migraine aura (if it exists), without any crisis treatment being taken.

Other secondary end points included the mean change in the score on the six-item Headache Impact Test (HIT-6) and the Migraine Disability Assessment (MIDAS). HIT-6 and MIDAS tests were designed to provide a global measure of adverse headache impact. HIT-6: scores range from 36 to 78, with higher scores indicating a greater degree of headache-related disability. MIDAS scores are interpreted as grade I = 0–5 (minimal or infrequent disability), grade II = 6–10 (mild or infrequent disability), grade III = 11–20 (moderate disability), grade IVa = 21–40 and higher (severe disability), grade IVb = 41 and higher (very severe disability) with higher scores indicating greater disability and decreased scores consistent with improvement. Safety and side-effect profiles were evaluated according to reported adverse events based on the material safety form provided to patients.

Study design

302 patients satisfying all the ICHD-3 inclusion criteria and none of the exclusion criteria were enrolled. Data collection was done after consent through an online evaluation form. Migraine diary assessment, HIT-6 and MIDAS were collected anonymously online before the start of treatment (baseline) and 3 months after use. 302 patients completed the first migraine assessment questionnaire, and 256 patients completed the second after 3 months of treatment (Figure 1). A material safety hotline has been set up to allow patients to report any incidents or side effects.

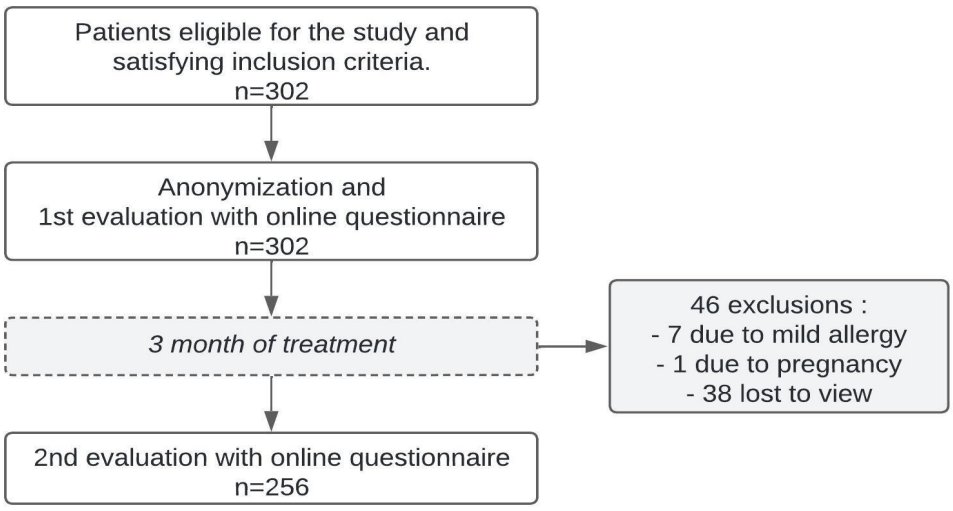

Figure 1: Study flow

Statistical analyses

The descriptive data are presented as mean ± SD between T0 (before starting the treatment) and T3 (after 3 months of treatment). A Q-Q plot was used to assess the suitability of the adjustment of the distribution. The Agostino and Pearson normality test was employed to reject the hypothesis of a normal distribution. A non-parametric Wilcoxon Signed Rank test was used to assess the difference observed between time T0 and T3. A p-value less than 0.05 was considered as statistically significant, with a Confidence Interval (CI) of 95%. Statistical analyses were performed in GraphPad Prism 9.1 (GraphPad Software, Inc., CA, USA).

Results

Primary endpoint

A total of 302 patients received treatment and completed the first migraine assessment questionnaire. 46 patients were unable to complete the second questionnaire. 7 patients due to mild allergy, 1 patient due to pregnancy and 38 other patients were lost to follow-up. 256 episodic migraine patients were analyzed whose demographic and baseline data are presented in table 1.

Table 1: Baseline characteristics of patients. Quantitative parameters are presented as mean ± SD.	
Male, n (%)	110 (43)
Female, n (%)	146 (57)
Mean age, years	36.4 years ± 4.2 years
Mean weight, kg	65 kg ± 8.3 kg
Mean height, cm	166 cm ± 9.1 cm
Mean no. of migraine days at T0	8.1 ± 2.5
Mean VAS score intensity (/10) at T0	7.3 ± 1.3
Mean migraine duration (hours) at T0	17.3 ± 7.1
Mean HIT-6 score at T0	53.1 ± 6.2
Mean MIDAS score (score; grade) at T0	18.1 ± 4.1 ; III

The primary endpoint was the change in the number of migraine days per month from time T0 to time T3 months of treatment. HERBA MIG showed a significant decrease in the number of migraine days -2.4 ± 0.2 (95%CI -2,80 to -1,96); p<0.001, this represents 28.4% reduction in migraine days per month (Figure 1).

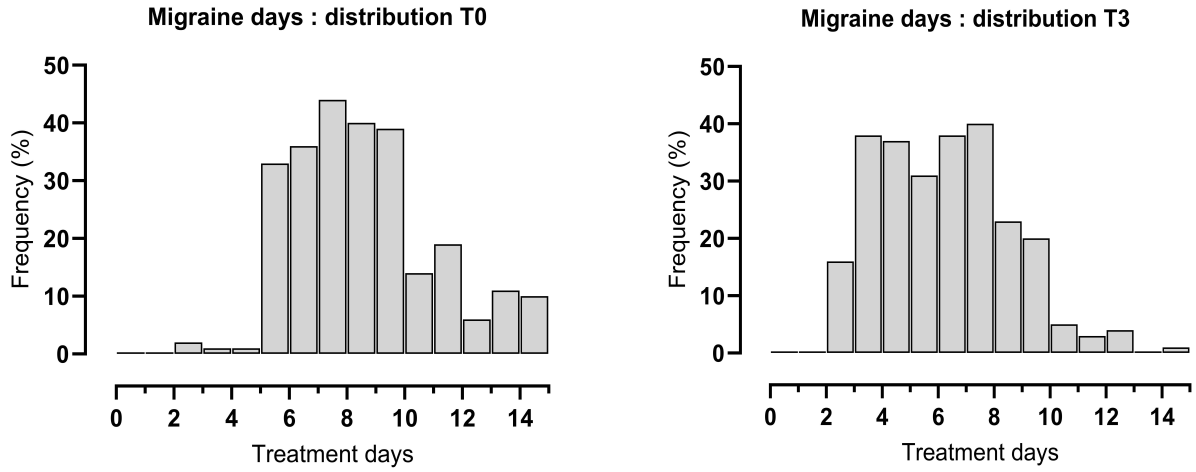

Figure 2: Percentage distribution of the number of migraine days at T0 (a) and T3 (b).

If we compare the frequency distributions of the two periods, the distribution is more spread out at time T0 in the interval [13-15] (Figure 2). This generates a final tail to the right from 10 days. In the histogram of the distribution at time T3, this tail tends to disappear with an accumulation in the interval (4 days, 8 days) covering almost the whole distribution. From 3 days to 5 days a new

interval appears andfrom 10 days almost no data is observed.

In other words, we have gone from a distribution with a long straight tail and a central moment close to the interval 6 days-10 days, to a distribution focused on the interval 4 days-8 days, with a shorter and less pronounced straight tail.

Secondary endpoint

The evolution of the intensity of migraines was evaluated on a numerical pain scale where 0 corresponds to no pain and 10 to an intolerable pain (Table 2). A significant decrease of -2.1 ± 0,1 ([95%CI – 2.39 to -1.83]; p<0.001) points was observed. The distribution of the migraine intensity score in the T3 period was more agglomerated in the interval (4 days-8 days) compared to (8 days-10 days) for the T0 period. In other words, the intensity of migraines was reduced. The median is 3 points shorter (8 *vs.* 5). In T3, a new interval (2 days,4 days) appears. In addition, the interval (4 days, 8 days) includes almost all the observations (Figure 3).

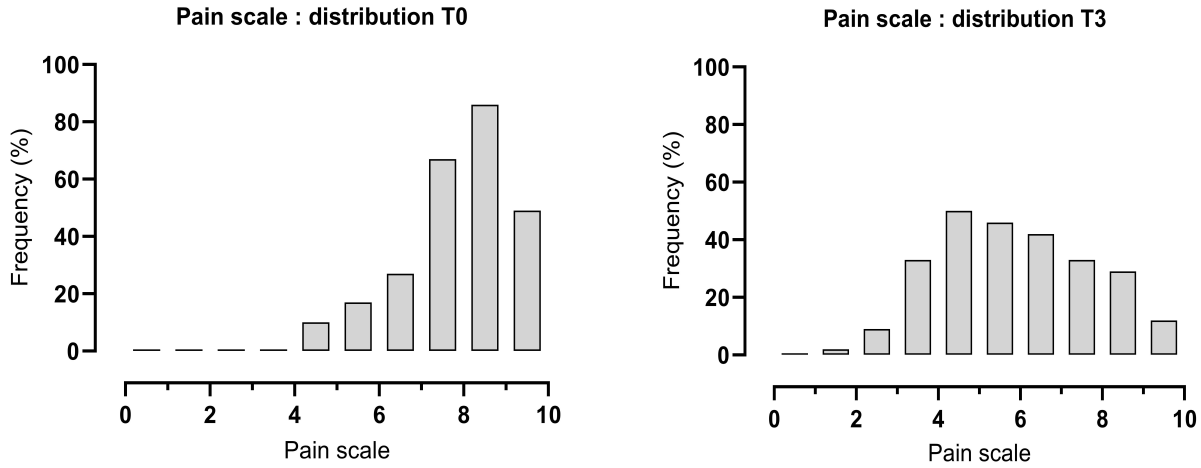

Figure 3: Percentage distribution frequency of pain assessment score at T0 (a) and T3 (b).

Table 2: Primary and secondary end points.

	T0	T+3 month	p-value	IC95
Migraine Days				
Mean value	8.1 ± 2.5	5.8 ± 2.4	<0.001	(-2.80 to -1.96)
Difference T0 *vs.* T3	- 2.4 ± 0.2			
Intensity				
Mean value	7.8 ± 1.4	5.7 ± 1.8	<0.001	(-2.39 to -1.83)
Difference T0 *vs.* T3	-2.1 ± 0.1			
Duration				
Mean value	17.3 ± 7.0	15.1 ± 6.9	<0.001	(-3.44 to -1.02)
Difference T0 *vs.* T3	-2.2 ± 0.6			
HIT-6				
Mean value	53.0 ± 6.2	48.2 ± 7.1	<0.001	(-5.97 to -3.65)
Difference T0 *vs.* T3	-4.8 ± 0.6			
MIDAS				
Mean value	18 ± 4.2	12.8 ± 5.4	<0.001	(-6.00 to -4.34)
Difference T0 *vs.* T3	-5.2 ± 0.4			

In the same way, the duration in hours of a migraine without any crisis treatment was evaluated. The evolution between the time of T0 and T3 shows a significant decrease of -2.2 hours ± 0.1 hours ([95%CI– 3.44 to -1.02]; p<0.001). These results are corroborated by the HIT-6 values, with a

significant reduction of 4.8 ± 0.6 ([95%CI -5.97 to -3.65]; p<0.001) points on the total score. Minimally Important Change (MIC) and Minimally Important Difference (MID) for HIT-6 were defined at -2.5 to -6 points for MIC and -1.5 points for MID. Although no MIC has been established for MIDAS, a preliminary analysis based on 25% change in monthly headache days estimated that an increase or decrease of 5 days of migraine-related disability per 3 months represents meaningful within-patient change (Carvalho *et al.* 2021). MIDAS test decrease of -5.2 days ± 0.4 days in treated patients compare to time T0 and T3.

Safety

A total of 7 patients reported mild allergy symptoms, that occurred within the first week of treatment. These adverse events were transient and self-limiting, resolving within 3 days-5 days without any treatment. It should be noted that 70% of patients reported a side effect consisting of browning of the urine. This side effect is completely normal, however, and is due to the *Tanacetum parthenium* plant. No serious adverse events were reported dur-ing the study.

Discussion

The results of this clinical study demonstrate that the dietary supplement HERBAMIG is effective in reducing the frequency, intensity, and duration of migraines in patients with episodic migraines. A reduction in migraine days per month by 29.6% is considered clinically meaningful, as a 30% reduction is often used as the threshold for a positive clinical outcome in migraine prevention trials [13]. Significant improvements in migraine-specific quality of life HIT-6 and disability MIDAS scores further support the clinical benefits of this dietary supplement [14].

The mechanisms by which HERBAMIG exerts its preventive effects are not fully elucidated, but may involve the phytochemical parthenolide, which has been shown to have anti-inflammatory and analgesic properties through TRPA1 and TRPV1 receptors [15,16]. Parthenolide has been shown to desensitize these receptors [17]. Moreover, evidence of activation of these receptors during migraine has been demonstrated on several occasions [8,17,18]. While the parthenolide hypothesis has been questioned, feverfew preparations standardized for parthenolide content have demonstrated efficacy in prior clinical trials [9,15,19]. Additionally, feverfew contains a complex mixture of pharmacologically active constituents, including flavonoids, sesquiterpene lactones, and essential oils, that may contribute to its anti-migraine effects through multitarget mechanisms [15,19,20].

A study by Pfaffenrath *et al.* on the ingredient *Tanacetum parthenium* MIG-99 showed that a dose of 6.25 mg extract, containing 0.5 mg Parthenolide (PTL) per day, reduced the number of migraine days by -1.8 after three months of treatment [21-24]. In comparison, HERBAMIG, with a reduction of -2.4 migraine days, is very well positioned thanks to the synergistic combination of its ingredients, notably salicin. HERBAMIG contains a smaller amount of parthenolide, 0.09 mg per day, but the presence of salicin potentiates the effect of PTL, as previously demonstrated [8]. This potentiation was observed in a mouse model of migraine, suggesting that the combination of the two ingredients in HERBAMIG could explain its increased efficacy despite a lower dose of PTL [25].

The inclusion of Salix alba (white willow bark) in the HERBAMIG formula may also enhance its anti-migraine properties. Salicin, the main active principle of willow bark, has long been used for the symptomatic relief of migraine and other types of headache [19]. In a migraine model, salicin was shown to potentiate the effect of parthenolide. The combination of parthenolide and salicin thus appears to be far more effective than parthenolide alone [8].

The precise mechanisms by which vitamins B2 (Riboflavin) and B12 (Cobalamin) may contribute to the anti-migraine effects of HERBAMIG are not yet fully elucidated. Riboflavin plays a crucial role in cellular energy production and has been shown to have neuroprotective properties, which may help alleviate migraine symptoms [14,11,22]. Cobalamin, on the other hand, is involved in the metabolism of neurotransmitters and myelin sheath formation, both of which are implicated in migraine pathogenesis. While the exact mechanisms are still under investigation, the inclusion of these B vitamins in the HERBAMIG formula may provide additional therapeutic benefits beyond the primary active ingredients, parthenolide and salicin.The use of coenzyme Q10 in migraine prevention still has limited evidence of its effectiveness in the literature. However, its potential role in mitigating migraine symptoms warrants further investigation. Coenzyme Q10 is involved in cellular energy production and has shown neuroprotective properties, which may be beneficial in alleviating migraine pathology [12,22].

The favorable safety profile observed in this study, with only mild and self-limiting adverse events such as allergic reactions (in 7 patients) that resolved within 3 days-5 days without any treatment,

strongly supports the tolerability and long-term use of HER-BAMIG for migraine prevention. The lack of any serious adverse events during the study further un-derscores the safety and acceptability of this dietary supplement for patients seeking a preventive option for their episodic migraines [26]. The limitations of this study are the lack of comparison with a placebo or reference treatment. In addition, an ITT analysis with intention-to-treat would have tempered the re-sults observed [27].

Conclusion

The results of this clinical study demonstrate that the dietary supplement HERBAMIG, containing a combination of feverfew, willow bark, riboflavin, cobalamin, and coenzyme Q10, is an effective and well-tolerated intervention for the prevention of episodic migraine. Further studies are nevertheless needed to better understand this efficacy and the mode of action of these ingredients.

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