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Review

Prevention of migraine in children and adolescents: results of an open-label study with special extract of *Petasites hybridus* root

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Introduction

Migraine is a genetic disease that has a major impact on life. Its prevalence is estimated to be 7.7% up to the age of 20. Preventive treatment of migraine in childhood and adolescence remains a challenge, due to the few studies conducted for this population and the presence of side effects in the use of the medications used.

Method

In this article, we evaluated the prospective open study conducted by Pothmann and Danesch using Petasites hybridus extract as a preventive treatment for migraine in children (6-9 years) and adolescents (10-17 years).

Results

This open study showed that at the end of the 4 months of treatment with Petasites hydbridus the reduction in migraine attacks in the total sample was 63.2%, 67% for children aged 6 to 9 years and 61.9% for adolescents aged 10 to 17 years. The overall response rate was 77.2%, with 85.7% for the 6- to 9-year-old group and 74.1% for the 10- to 17-year-old group. There was also a reduction in the mean duration of attacks in 62.7% of patients, from approximately 10 hours to 7 hours. No significant side effects were observed.

Conclusion

Petasites hybridus proved to be a safe and effective option for the preventive treatment of migraine in children and adolescents.

Keywords:
Preventive migraine treatment
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Introduction

Migraine is a genetically determined primary headache that affects about 15% of the world's population. Its occurrence can happen during any period of life, and can begin in childhood or adolescence, but also in adulthood. Its diagnosis is based on the criteria established by the International Headache Society (IHS) in its classification system, currently in its 3rd edition (1).

Migraine is a disease with a strong hereditary component, and it is estimated that between 35% and 60% of sufferers have family members who also suffer from the condition (2). Despite this, many children and adolescents who show symptoms of the disease end up having a delayed diagnosis, which delays the start of appropriate treatment. In clinical practice, it is common to observe cases in which parents with migraine do not associate their children's headaches with the same condition they have.

Although the disease is known and diagnosed by its painful symptoms, it also has non-painful symptoms such as fatigue and cognitive changes (irritability and difficulty concentrating), appetite changes and daytime sleepiness, gastrointestinal symptoms such as nausea and abdominal pain. In many patients, these symptoms, especially in childhood, can contribute significantly to the disability generated by the disease (3).

In a comprehensive systematic review on the prevalence of headaches and migraine conducted by Abu-Arafeh et al. (4), it was found that the prevalence of headaches up to 20 years of age is 58.4% (based on 38 studies and 80,876 children). Females had a 53% higher risk of developing headache. The overall prevalence of migraine was 7.7%, being 9.7% among women and 6.0% among men, representing a 67% higher risk for women.

When stratified by age group, the prevalence of migraine was lower in both sexes up to 14 years of age but increased by 2.7% in women and 2.5% in men up to 20 years of age (4).

It is estimated that between 8% and 30% of these children and adolescents will experience recurrent and frequent headaches, characterized by episodes that occur at least once a week (5). These patients may benefit from preventive treatment. In addition to the frequency of crises (3 or more days of pain per month), other indications for preventive treatment include: lack of response to acute treatment due to ineffectiveness or side effects, prolonged crises (greater than 24 to 48 hours) or intolerable crises for the patient (5).

The preventive treatments available for migraine are mostly adapted from protocols used in adults. Clinical studies comparing these drugs with placebo as migraine preventatives in childhood and adolescence have not demonstrated significant superiority of the active drugs over placebo, and the response to placebo is usually high in the treatment of migraine (6). However, the association between cognitive-behavioral therapy and the active engagement of patients and their guardians in the choice of treatment can significantly increase therapeutic efficacy (7).

The use of herbal medicines in the preventive treatment of migraines in children and adolescents is an alternative that deserves consideration, and the data in the article in question will be analyzed.

Petasites hybridus, known as butterbur, is a plant native to Europe that grows in moist areas such as stream banks. With a long history of medicinal use since antiquity, its therapeutic properties have been rediscovered since the last century. Petasites hybridus has spasmolytic and analgesic effects, and is used in the management of conditions such as migraine, asthma, urinary tract spasms, and back pain. These benefits are mainly attributed to the presence of sesquiterpenes, especially petasins, S-petasin, and isopetasin (8, 9).

Mechanism of action

The action of *Petasites hybridus* is mainly attributed to sesquiterpenes, S-petasin, and isopetasin, as well as other components such as volatile oils, flavonoids, and tannins. Among these, S-petasin, a sesquiterpene ester, is presumed to be the main active component, exerting clinically significant analgesic effects through anti-inflammatory actions, including inhibition of leukotriene biosynthesis (10).

In the context of migraine, Benemei et al. (11) investigated the ability of isopetasin to interact with transient receptors of anserine potential type 1 (TRPA-1). The study used human and rodent cells expressing TRPA-1 to evaluate calcitonin gene-related peptide (CGRP) release in the spinal cord and meningeal blood flow in rats. The results showed that isopetasin, when used alone and in single use, activates TRPA1. It is worth remembering that, physiologically, TRPA-1 mediates inflammation by the release of substance P and CGRP. This inflammatory action, however, can be inhibited by exposure of the receptor to isopetasin. When used for a long time, isopetasin has also been shown to desensitize TRPV1 and TRPV4 receptors (11). Thus, it was concluded that isopetasin acts as a TRPA1-targeted agent, promoting desensitization of trigeminal peptidergic terminals, reducing CGRP release and, consequently, pain signaling.

Other potential mechanisms of action include modulation of calcium channels and selective inhibition of cyclooxygenase 2 (COX-2) receptors. In vitro studies have shown that extracts of *Petasites hybridus* inhibit COX-2 and PGE2 release, acting directly on the enzyme and preventing activation of the MAP kinase p42/44 pathway in primary microglial cells of rats (12).

Rational

Two studies evaluating approximately 290 adult patients were conducted demonstrating the safety and efficacy of using *Petasites hybridus* in migraine prevention (13, 14). Pothmann and Danesch conducted an open-label study to evaluate its efficacy in children and adolescents (15).

Methods

Between April 1998 and July 2002, 112 patients were included in a prospective, open-label study conducted in five pediatric clinics.

The study population consisted of 29 children between 6 and 9 years of age and 79 adolescents between 10 and 17 years of age. Participants were diagnosed based on the International *Headache Society* classification criteria (1) and included those with a history of migraine for at least one year, with at least 3 episodes per month and/or severe attacks lasting 12 to 24 hours in the three months prior to inclusion in the study, or attacks considered intolerable.

Patients who had been on preventive treatment in the three months prior to the study, who had a history of good previous response to *Petasites hybridus* as a preventive for migraines, or who had concomitant conditions that could interfere with the evaluation were excluded (Table 1).

Table 1

Criteria	
Inclusion	Exclusion
At least 1 year of history of Migraine	Use of medication
Minimum of 3 attacks per month in the 3 months	Previous use of butterbur as a preventive
Attacks lasting more than 12 hours	People with serious diseases

Study participants were treated with 25 mg capsules containing an extract of the *petasites* hybridus rhizome, with a minimum of 15% petasins. Dosage was determined by the investigator, following the recommendations below:

• Months 1 and 2:

- Children 6 to 9 years: 1 capsule of 25mg 2 times daily.
- Adolescents 10 to 17 years: 2 capsules of 25mg 2 times daily.

• Months 3 and 4:

- Patients considered responders maintained the initial dose.
- Non-responders had their dose adjusted to:
- Children 6 to 9 years: 1 capsule of 25mg 3 times daily.
- Adolescents 10 to 17 years: 2 capsules 25mg 3 times daily.

Participants recorded their intake of the drug in a diary and follow-up visits were conducted in the 2nd and 4th month after starting treatment.

In addition to recording the use of the medication, the diary, designed specifically for children, included information on pain characteristics such as frequency, duration, and intensity (on a 1-10 visual scale), the severity of associated symptoms, the impact on physical ability (on a 4-point verbal scale), and global impairment (on a 10-point visual scale). Also recorded were a clinician and patient-rated efficacy scale, the use of concomitant medications, and any adverse events or side effects, which were actively investigated and documented at each visit.

The primary variables for assessing the efficacy of *Petasites hybridus* as a prophylactic drug included the frequency and duration of migraine attacks, as well as the rate of treatment responders.

The mean age of the 6-9 years-old group was 8.0 ± 0.9 years and of the 10-17 years-old group was 12.3 ± 1.9 years, with 55.2% boys in the first group and 54.4% boys in the second group. Of the total sample, 76.9% had migraine without aura. The mean duration of migraine attack in months before inclusion in the study was 25.9 ± 14.4 months for those aged 6-9 years-old and 37.9 ± 20.6 months for participants aged 10-17 years-old. There was no difference between the groups in the number of migraine attacks in the last 3 months (9.4 ± 8.5 vs 9.7 ± 10 attacks), nor in the duration of migraine attacks in hours (9.6 ± 12.2h vs 10.2 ± 10.8h). Complete characteristics can be analyzed in the original publication.

Results and Discussion

At the end of the 4 months of treatment, the reduction of migraine attacks in the total sample was 63.2%, being 67% for children aged 6 to 9 years and 61.9% for adolescents aged 10 to 17 years. The overall response rate was 77.2%, with 85.7% for the 6-9 age group and 74.1% for the 10-17 age group. There was also a reduction in the mean duration of migraine attacks in 62.7% of the patients, from about 10 hours to 7 hours. However, approximately 25% reported longer atacks.

In the overall evaluation carried out by parents and patients, 81.6% reported a great improvement in migraine at the end of treatment with Petasites hybridus. Another important observation was the reduction in the number of severe headaches. Compared to baseline, the reduction was from a median of 9 to 2 days in the 6 to 9 years old group and from 8 to 2 days in the 10- to 17-year-old group.

In addition, 91.8% considered the tolerability to be good, feeling the same or better than before the start of

treatment. Only 7.4% (8 patients) reported mild adverse events, such as eructation (4 cases), nausea (1 case), and abdominal pain (1 case), none of which led to the interruption of the study.

Although this study is open-label and without a comparative arm, the results observed are consistent with those of two randomized, double-blind placebo studies.

Comparison to Controlled Studies

In randomized double-blind studies conducted with adults, Petasites hybridus has also demonstrated efficacy.

A double-blind, randomized, placebo-controlled study conducted by Lipton et al. (13) evaluated 245 adult patients with episodic migraine, characterized by 2 to 6 monthly migraine attacks. Participants were randomly assigned to three treatment groups for 4 months: Petasites hybridus 75 mg twice daily, Petasites hybridus 50 mg twice daily, or placebo. The main objective of the study was to measure the reduction in the frequency of migraine attacks at the end of the treatment period compared to the three months prior to recruitment (13).

The results indicated that the group treated with Petasites hybridus 75 mg twice a day showed a 48% reduction in migraine frequency, while in the group that received 50 mg twice a day the reduction was 36%. In the placebo group, the reduction was 26% ($p<0.0012$ for the comparison between 75 mg 2x daily and placebo). In addition, the proportion of patients who achieved at least a 50% reduction in migraine frequency was 68% in the Petasites hybridus 75 mg twice daily group, compared to 49% in the placebo group ($p<0.05$) (13). No significant side effects were identified, only increased eructation (13).

Another study, also double-blind, randomized and placebo-controlled, was conducted with 60 adult patients diagnosed with episodic migraine, characterized by at least 3 monthly attacks (14). The sample was divided into two groups: 33 patients received butterbur hybridus at a dose of 50 mg twice a day, while the others received placebo. After three months of treatment, the mean frequency of migraine attacks per month decreased from 3.9 to 1.8 in the group treated with butterbur ($p<0.0024$). In the placebo group, the reduction was smaller, from 2.9 to 2.6, without reaching statistical significance. The response rate, defined as a greater than 50% reduction in migraine attacks frequency, was 45% in the petasites-treated group and 15% in the placebo group. However, placebo-controlled studies in pediatric and adolescent populations are still scarce, often presenting uncertain responses and small sample sizes (14).

When comparing the results of the randomized, double-blind, placebo-controlled studies of Lipton et al. (13) and Diener et al. (14) with the study in question, a higher response rate for the open-label study is observed, something frequently reported in open-label studies. For example, in adults treated with Petasites hybridus extract (75 mg 2x), there was a 51% reduction in migraine frequency after four months, compared to 32% in the placebo group. The response rate was 68% in the group treated with butterbur and 49% in the placebo group.

In the present open-label study, conducted with children and adolescents, the reduction in migraine attacks frequency ranged from 61.9% to 67%, and response rates ranged from 74.1% to 85.7%, surpassing the results observed in adults and compared to a randomized trial with flunarizine in children, which showed a response rate of 66% (16).

However, it is important to consider that randomized, placebo-controlled studies generally apply stricter inclusion and exclusion criteria and tend to be shorter in duration, which often limits the representation of clinical reality.

Impact of migraine and the treatments used

In addition to painful crises, the symptoms associated with migraine, such as inattention, irritability, mood swings, anxiety, depression, and fatigue, have a significant impact, especially on school-age children. These symptoms can affect learning, socialization, and emotional development (3). Thus, the choice of treatment should consider not only the effectiveness in preventing the migraine attacks, but also the safety profile and possible side effects.

Medications such as topiramate, flunarizine, amitriptyline, and propranolol, often used to prevent migraine, have significant side effects, such as drowsiness, weight gain, mood depression, and cognitive impact, which can aggravate patient impairment (17).

Safety and Tolerability of Petasites hybridus

Studies with Petasites hybridus have not shown serious side effects. The main complaint was eructation, which was mild and rare. There were no reports of serious adverse events or treatment interruptions due to side effects. The concern about hepatotoxicity related to pyrrolizidine alkaloids is mitigated by the extraction process used, which meets German pharmacovigilance standards (15).

Conclusion

The study reinforces the potential of Petasites hybridus as a safe and effective option in migraine prevention in children and adolescents, highlighting its good tolerability and safety profile.

Although this is an open-label study with no comparative arm, the findings of this study are very similar to those

found in two randomized, double-blind, placebo studies. The overall impression of the study investigators and patients/family members agrees with what was observed in the results obtained through the headache recording, that the most marked improvement was observed for the frequency of pain, rather than for intensity or duration.

In addition, it points to the importance of real-world studies as a complementary tool to controlled trials, providing valuable data for clinical practice. The choice of preventive treatment should consider not only the reduction of crises, but also the overall impact of the disease and the side effects of available therapies.

Considering that the study was published in 2005 and the data were collected between 1998 and 2002, we could risk saying that this study was anticipated in time, being done along the lines of what we now call a real-world study, a trend widely used and accepted today as an alternative to randomized double-blind, placebo controlled studies. We cannot say that they are exclusive, but complementary, since real-world studies provide valuable information about the evolution of patients in a non-restrictive setting such as controlled studies, often enabling the generation of data that would not be feasible in a controlled study.

Within real-world studies, we can conduct interventional studies, with monitoring that follows care practice, with or without placebo, and which will generally recruit for a longer period. It should be emphasized that they may present greater bias related to recruitment, data recording and the fact that the evaluator is not blinded (18), while randomized studies with placebo are much more restricted in their inclusion and exclusion criteria and tend to be of shorter duration, often not representing real life.

Another important point to be highlighted was the tolerability of butterbur when compared to other medications used in the prevention of migraine for children and adolescents. As already mentioned, studies carried out with drugs such as topiramate, amitriptyline, flunarizine and propranolol are few, but side effects are abundant (6).

We must turn our attention to the non-painful symptoms of migraine and its impact, especially for the school-age population. Cognitive symptoms such as inattention, changes in mood, with irritability and anxious and depressive symptoms, change in physical disposition, with a real impact on their ability to socialize and interact are already present in the routine of migraine patients. The choice of treatment in this very peculiar phase of learning, forming relationships and discovering the world must also consider these aspects.

In conclusion, Petasites hybridus proved to be an effective and safe option in the preventive treatment of migraine in children and adolescents between 6 and 17 years of age in an open study.

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