ALTERNATIVES IN PAIN MANAGEMENT

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Pediatric migraine sufferers and alternative therapies

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Abstract

Introduction: Migraine is a common pediatric disorder, which results in chronic pain. Because of the limited effectiveness of conventional drug regimens, an increased number of pediatric patients look for an alternative medication regimen to prevent and treat migraines.

Method: Search terms "pediatric, headache, migraine, treatment, alternative treatment" were used. Butterbur and riboflavin are suggested as alternative remedies for migraine prophylaxis, and a combination of feverfew and ginger for acute treatment. In addition to previous search terms, "butterbur, riboflavin, feverfew, ginger" were used to review their effectiveness.

Result: Butterbur or riboflavin may be an appropriate alternative regimen to prevent migraine, and a combination of feverfew and ginger may be an option for acute episode.

Conclusion: Study results are promising, but not yet conclusive. Study samples are relatively small. These alternative regimens may benefit pediatric migraine sufferers, but they should be carefully monitored to evaluate individual efficacy when in use.

Keywords: pediatric, migraine, alternative medicine, butterbur, feverfew, riboflavin, ginger

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Migraine is an episodic disorder characterized by headache, photophobia, phonophobia, nausea, and/or muscle pain, which temporarily disables physiologic and cognitive function. It may be preceded by a perceptual disturbance called an *aura*, and symptoms may last from hours to days.[1-3] Migraine is a major source of chronic pain in pediatrics; its prevalence rates are 3% in infancy and increase up to 23% in adolescence.[4] When the intensity and frequency of migraine attacks are not controlled, it negatively affects quality of life by reducing a child's functionality (eg, best rest). It reduces school attendance rates and possibly affects future career opportunities.[3,5,6]

For frequent migraines, a conventional prophylactic drug regimen, such as a beta-blocker, antidepressant, or antiseizure medication, is prescribed as a preventive measure.[3,7] However, its efficacy is limited, demonstrating only a 20% to 40% response rate.[3] During an acute episode, acetaminophen, aspirin, and caffeine combination products; nonsteroidal anti-inflammatories; triptans; ergot derivatives; or various opioid- and butalbital-containing products are used as conventional regimens to terminate the migraine attack.[1,3,7] These abortive medications relieve pain from moderate to severe migraine in 65% of patients, and 40% report no pain 2 hours after the medication was administered.[1] Thus, alternative regimens for migraine prophylaxis and treatment are needed to improve therapeutic outcomes and quality of life in children. Notably, butterbur and riboflavin are suggested as alternative remedies for migraine prophylaxis and a combination of feverfew and ginger is recommended for acute treatment.

Butterbur

Butterbur, *Petasites hybridus*, a native European perennial shrub, belongs to the Asteraceae family. It is found in Europe, parts of Asia, and North America, along riversides, streams, and other marshy areas.[3,6,8] Butterbur has been used as a treatment regimen for fever, spasm, and pain in parts of Europe and Asia for many years and is currently used as an herbal remedy for migraine prophylaxis. Butterbur regulates calcium channels, inhibits leukotriene biosynthesis and lipoxygenase pathway, and ultimately reduces inflammation associated with migraine.[8,9]

Studies have been conducted to evaluate whether butterbur's anti-inflammatory properties would benefit pediatric migraine sufferers. An open-label, prospective study conducted in pediatrics supported the use of butterbur to benefit young migraine sufferers.[6] A total of 108 patients, 29 children (ages 6-9 years) and 79 adolescents (ages 10-17 years), were observed during a 4-month period. These patients had experienced migraines for at least a year, with minimum frequency of 3 migraines per month over a 3-month period before the study or with significant degree of severity and duration. During the first and second months, children received 25 mg twice daily and adolescents received 50 mg twice daily. Patients who experienced at least 50% reduction in monthly migraine attack frequency were considered responders and continued the initial regimen during the third and fourth months. Nonresponders received an additional dose. During the third and fourth months, nonresponsive children received 25 mg 3 times daily, and nonresponsive adolescents received 50 mg 3 times daily.

Efficacy was evaluated by attack frequency, duration, and severity after 4 months of treatment. Eighty-six percent of children and 74% of adolescents responded to the treatment, and 82% of patients reported considerable improvement. The frequencies of migraine attacks in children and adolescents were reduced by 67% and 62%, respectively. The duration of migraine attacks was reduced from 10 to 7 hours on average. Sixty-seven percent of the children and 62% of the adolescents experienced the shortened duration of attacks. However, 27% of the children and 25% of the adolescents experienced the prolonged durations of attacks. Sixty-seven percent of the children and 49% of the adolescents reported reduced severity of migraine attacks. No serious adverse events were reported. Seven percent of patients experienced adverse events, including eructation, nausea, and abdominal pain. Although butterbur's observed therapeutic benefits are promising, further controlled studies in pediatrics are needed to determine a more-direct correlation to this positive therapeutic outcome.

A prospective, randomized, controlled study on butterbur was conducted and had a similar conclusion.[5] The study consisted of the following phases: an 8-week baseline phase, a 12-week treatment phase, an 8-week posttreatment phase, and an 8-week follow-up phase at 6 months after treatment completion. Patients (ages 8-12 years) who experienced migraine for at least a year with a minimum frequency of 2 migraines per month in the past 3 months before the study were included. The patients were observed for 8 weeks to document a baseline for attack frequency and headache intensity. Twenty patients were randomly assigned to the butterbur treatment group and 19 patients to the placebo group.

Similar to the previous study, patients younger than 10 years received butterbur at 25 mg twice daily, and patients 10 years and older received butterbur at 50 mg twice daily. After 8 weeks of the treatment, if the patient was satisfied with the reduced number of attacks, the patient continued the initial regimen for the remaining 4 weeks of the treatment phase. If the patient was not satisfied with the reduced number of attacks, and relief was only marginal, patients younger than 10 years received 75 mg/d and patients 10 years and older received 150 mg/d until the treatment was completed. Eight patients both in the treatment and the placebo group received raised dosages per day.

During posttreatment and the follow-up period, patients on a stable dosage regimen in both groups reported a greater reduction of attack frequency, and the effect was more pronounced in the treatment group. From the beginning of the baseline phase to the end of the posttreatment phase, patients were asked to report migraine attack severity, onset time, duration, associated symptoms, and adverse events, which were assessed monthly. The primary and secondary efficacies were evaluated at the end of the 8-week posttreatment period and the 8-week follow-up phase. The primary efficacy measured the percentage of reduction in monthly migraine attack frequency from baseline to posttreatment and follow-up. The secondary efficacy evaluated headache intensity relief by at least 50% from baseline to posttreatment and follow-up.

In the posttreatment phase, the frequency of migraine attacks in the butterbur treatment group and placebo group were reduced by 36% and 29%, respectively. Although the reduction percentage was higher in the butterbur treatment group, there was no statistical significance ($P = .159$). In the follow-up phase, the frequency of migraine attacks in the butterbur treatment group were reduced by 59% and placebo group by 31%, and the result was statistically significant ($P = .044$). The greater efficacy during the follow-up may have been due to delayed full-dose effect.

For the secondary efficacy, the intensity of relief was not statistically significant in both posttreatment and follow-up ($P = .505$ for posttreatment and $P = .793$ for follow-up). During the treatment, 15 patients in the butterbur group reported 42 adverse events, and 15 patients in the placebo group reported 44 adverse events. Adverse effects reported in the butterbur group were generally mild and included nausea, mild diarrhea, abdominal pain, regurgitation, bitter taste sensation, itching, rash, and allergic rhinitis. In conclusion, this clinical data provided evidence of the therapeutic efficacy of butterbur in migraine prophylaxis by demonstrating greater migraine-attack reduction compared with the placebo group. To strengthen the evidence, more placebo-controlled studies with larger pediatric populations and longer treatment durations are suggested.

Riboflavin

Riboflavin, vitamin B2, is another alternative remedy suggested for migraine prophylaxis in pediatrics. Riboflavin is a precursor of flavin mononucleotide and flavin adenine dinucleotide, which are involved in oxidation-reduction reactions of the mitochondrial electron transport chain. Riboflavin use is based on the hypothesis of migraine pathogenesis related to mitochondrial dysfunction. Taking riboflavin (100-200 mg/d) may improve mitochondrial energy reserves and mitochondrial function and, in return, may reduce migraine frequency and the use of abortive treatment.[4,7]

A study was conducted to investigate the effectiveness of riboflavin on migraine prevention in the pediatric population.[4] In this study, 41 pediatric patients, with a mean age of 13 years (range, 8-18 years) participated. These subjects experienced prophylactic treatment failure, suffered from a minimum frequency of 3 moderate to severe migraine attacks or 2 severe ones, and were not exposed to prophylactic treatment in the 3 months before the study. The study was designed in 3 phases: a baseline phase without prophylactic medications, a treatment phase, and a follow-up phase. Patients were randomly assigned to receive 200 mg or 400 mg of riboflavin per day for 3, 4, or 6 months and were followed, on average, for 18 months.

The study result supported that the use of riboflavin in pediatric patients reduced migraine frequency and migraine intensity. Riboflavin use significantly lessened the severity of migraine attacks, reduced the number of attacks and the use of abortive regimens, and improved the effectiveness of abortive regimens. The 3-month treatment group showed a 9% reduction in the mean attack frequency from baseline through the treatment phase and a 14% reduction through the follow-up phase ($P < .01$). The 4-month treatment group showed a greater reduction of mean attack frequency of 15% from baseline through the treatment phase ($P < .01$). Although the 6-month treatment group showed an 8% reduction of mean attack frequency from baseline through the treatment phase, that was not statistically significant ($P > .05$). Overall, in the treatment phase, 3-, 4-, and 6-month treatment groups showed at least a 50% reduction in migraine attack frequency: 43%, 83%, and 45%, respectively.

In the severity of the migraines, the 3-month treatment group showed a statistically significant decrease during the treatment phase and follow-up phase ($P < .01$). However, the 4-month and 6-month treatment groups showed no statistically significant reduction in severity ($P > .05$). Thirteen percent of patients in the 3-month treatment group did not require abortive treatment during the treatment and follow-up periods, and 68% of patients in the 3-month treatment group reported that their abortive treatments were more effective. Mild adverse effects included coloration of the urine, vomiting because of taste, and increased appetite. No significant differences in responses between the patients who received 200 mg/d and those who received 400 mg/d were reported. Thus, the study results showed the effectiveness of riboflavin for migraine prophylaxis in the pediatric population with good tolerability. The study result needs to be interpreted with a degree of caution because there was no placebo group used for comparison.

A Combination of Feverfew and Ginger

Feverfew, *Tanacetum parthenium*, is a member of the Asteraceae family, whose leaves are used to make commercially available products. Despite some controversies on the efficacy of feverfew, it has been used as an alternative regimen for migraine prevention because of its anti-inflammatory properties. Feverfew inhibits platelet aggregation, inhibits prostaglandin and phospholipase A synthesis, and releases serotonin from platelets and white blood cells. Ginger is a naturally occurring compound. It inhibits prostaglandin as well and also inhibits leukotriene synthesis. Recently, feverfew and ginger together have been suggested as an abortive regimen.[9]

To evaluate its effectiveness on acute migraine episodes, a randomized, double-blinded, placebo-controlled study was conducted at 3 sites using LipiGesic® M (PuraMed BioScience, Schofield, WI), a sublingual feverfew and ginger product.[1] Although study subjects did not exclusively represent a pediatric population, inclusion of pediatrics can provide important insights. There were 5 pediatric patients out of 59 participants, and all subjects were between 12 and 60 years with 2 to 6 attacks per

month over the previous 3 months. These patients had at least a year of migraine history and experienced 75% of migraine attacks progressing from mild to moderate and severe severity. Subjects were randomly assigned to receive a combination of feverfew and ginger or placebo. Patients in a treatment group were instructed to take 2 unit dose applicators at the onset of migraine and to take an additional 2 unit doses for their persistent migraine at 1 hour.

The study results supported a combination of feverfew and ginger as an alternative treatment for pediatric migraine. Thirty-two percent of subjects in the treatment group and 16% of patients in the placebo group reported having no pain 2 hours posttreatment ($P = .02$). These groups demonstrated statistically significant responses related to associated migraine symptoms and headache characteristics at 2 hours posttreatment. Patients in the treatment group responded more favorably with decreased pulsating sensations ($P = .007$), nausea ($P = .002$), light sensitivity ($P = .001$), and sound sensitivity ($P = .003$); they also had a lesser degree of severity ($P = .015$) but reported more incidences of nausea and oral numbness. Most adverse events were mild, indicating the combination of feverfew and ginger was well tolerated. Although the study results support the use of a combination of feverfew and ginger as an abortive therapy, it only partially represented the pediatric population. To demonstrate its efficacy in pediatric migraine suffers, a controlled study in an exclusively pediatric population would be required.

Conclusion

The prevalence of herbal and dietary supplement usage among those ages 4 to 17 years in 2007 was 3.9%, involving 2.9 million of the pediatric population.[10] Currently more than 15 000 herbal medications are available in the United States, and 5% of the pediatric pain management programs provide herbal medicine along with conventional treatment.[11] Migraine is a chronic condition, for which pediatric patients are increasingly using an alternative regimen to prevent and treat migraine symptoms. As shown above, butterbur or riboflavin may be an appropriate alternative regimen to prevent migraine and a combination of feverfew and ginger may be an option for acute episode. However, these treatments should be used with caution. Study results shown above are promising but not yet conclusive. Study samples are relatively small. These alternative regimens may benefit pediatric migraine sufferers, but those patients should be carefully monitored to evaluate individual efficacy when the treatments are in use.

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