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Research Submission

Use of a Pine Bark Extract and Antioxidant Vitamin Combination Product as Therapy for Migraine in Patients Refractory to Pharmacologic Medication

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Objective.—To evaluate the potential benefit of a pine bark extract and antioxidant vitamin combination product in the treatment of migraine headache.

Background.—This was an uncontrolled preliminary study to investigate the potential of an antioxidant formulation as therapy for migraine headache.

Methods.—Twelve patients with a long-term history of migraine with and without aura who had failed to respond to multiple treatments with β-blockers, antidepressants, anticonvulsants, and 5-hydroxytryptamine receptor agonists were selected for the study. They were treated with 10 capsules of an antioxidant formulation of 120 mg pine bark extract, 60 mg vitamin C, and 30 IU vitamin E in each capsule daily for 3 months. Following enrollment patients completed a migraine disability assessment (MIDAS) questionnaire to give a baseline measure of migraine impact on work, school, domestic, and social activities over the previous 3 months. Patients were then treated for 3 months with the antioxidant formulation while continuing to receive existing pharmacologic medications. A second MIDAS was given at the conclusion of the treatment period.

Results.—There was a significant mean improvement in MIDAS score of 50.6% for the 3-month treatment period compared with the 3 months prior to baseline ($P < .005$). The treatment was also associated with significant reductions in number of headache days and headache severity score. Mean number of headache days was reduced from 44.4 days at baseline (95% CI 28.9 to 59.8) to 26.0 days (95% CI 5.3 to 46.7; $P < .005$) after 3 months' therapy and mean headache severity was reduced from 7.5 of 10 (95% CI 6.7 to 8.4) to 5.5 (95% CI 4.1 to 7.0; $P < .005$).

Conclusion.—These data suggest that the antioxidant therapy used in this study may be beneficial in the treatment of migraine possibly reducing headache frequency and severity. Further clinical investigation into the efficacy of antioxidant as therapy for chronic migraine is warranted.

Key words: migraine, antioxidant, pine bark extract, MIDAS

Abbreviations: MIDAS migraine disability assessment, 5-HT 5-hydroxytryptamine, IU international unit, NF-κB nuclear factor-kappa B, SD standard deviation

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The major classes of the medications for migraine prevention are β-blockers, calcium channel blockers, tricyclic antidepressants, anticonvulsants, and nonsteroidal anti-inflammatory drugs (NSAIDs). There are multiple mechanisms of actions on which the preventive agents act. β-Blockers are thought to interact with 5-hydroxytryptamine (5-HT) or serotonin receptors and cross-modulation of the serotonin

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system.[1] Calcium channel blockers block intracellular calcium entry and cellular depolarization.[2,3] Tricyclic antidepressants block reuptake of 5-HT at central sites.[4,5] Few anticonvulsants have been approved for migraine prevention. Valproate is thought to alleviate migraine via stimulation of gamma-aminobutyric acid (GABA) synthesis and inhibition of GABA degradation.[6,7] Gabapentin alleviates migraine by interacting with $\alpha_2\delta$-subunit of the calcium ion channel and increasing the concentration and possibly the rate of synthesis of GABA.[7,8] Topiramate alleviates migraine by potentiating GABA inhibition, blocking voltage-sensitive sodium ion channels, and antagonizing non-NMDA glutamate excitatory receptors.[8,9] NSAIDs inhibit prostaglandin and leukotriene synthesis and inhibit the neurogenic inflammation of migraine.[10,11] To date, the response rates achieved with β-blockers, tricyclic antidepressants, anticonvulsants, and other prophylactic agents often are inconsistent and rarely exceed 55% to 65%, and nonpharmacological approaches can be equally effective strategies in the treatment of migraine.[12-14]

Treatment and management of migraine is complicated by the variability of response, suggesting that the pathophysiology of migraine is complex. There are many peripheral and central factors involving the nervous system that may trigger migraine attacks.[15] Recent evidence implicates oxidative damage caused by free radicals in the brain as playing another possible role in the pathogenesis of migraine headache. The most convincing evidence for free radical activity comes from nitric oxide, which is a potent vasodilator and is an important biochemical in the trigeminal-vascular peripheral mechanism of migraine headache.[15,16] Furthermore, studies have shown that platelet levels of nitric oxide, as well as nitric oxide metabolites such as nitrate/nitrite, are increased in migraineurs and rise further during attacks.[17,18] Therefore, free radical scavengers may provide a potential molecular basis for prophylactic antimigraine therapy by neutralizing nitric oxide overproduction and possibly preventing formation of highly toxic peroxynitrite. The aim of the present study was to evaluate the potential benefits of a potent antioxidant formulation in the treatment of migraine headache.

The antioxidant formulation in this study was chosen to contain three antioxidant components. Vitamins C and E were included as being well established dietary antioxidants with widely accepted health benefits, and a pine bark extract, was included as a flavonoid component, rich in proanthocyanidins that has demonstrated potent in vitro antioxidant activity and proven safety in clinical trials.[19] Although there is a paucity of data to provide an experimental foundation for use of flavonoids as therapy for migraine, flavonoids have a remarkable tolerability profile and display a wide range of biochemical and pharmacologic activities that strongly suggest a role in promoting health and preventing disease.[20] The pine bark extract has been found to be safe and well tolerated with no evidence of change in glycemic control, renal and liver function, and hematological parameters.[21]

PATIENTS AND METHODS

This was an uncontrolled, open-label study of 3 months' duration. For inclusion, patients had to have a long-term history of migraine with and without aura diagnosed according to International Headache Society (IHS) criteria.[22] Patients had failed to respond to multiple treatments of β-blockers, antidepressants, anticonvulsants, or 5-HT receptor agonists after taking the drugs for an adequate period of time at an adequate dose. The patients with the diagnosis of medication overuse according to the IHS criteria of medication overuse[23] were excluded from the study. In order to reliably self assess the impact of migraine in terms of keeping daily headache diaries and number of days of lost and limited activity, patients were selected that were likely to comply with the necessary record keeping. No changes in patients' medications were made during the study and patients were instructed to keep taking their medications. Written informed consent was obtained from each patient.

Patients received a supply of the antioxidant combination product every month for 3 months and were instructed to take 10 capsules/day in the morning. Each capsule contained 120 mg of Enzogenol®, a flavonoid-rich, commercial pine bark extract, 60 mg of vitamin C, and 30 IU of natural vitamin E. Patients were evaluated during monthly visits where they received

a neurological examination and were questioned about adverse events and headache records. Patients were assessed for migraine impact before and after the treatment period using migraine disability assessment (MIDAS) questionnaire.[24] This comprised 5 scoring questions to assess the number of days of lost or limited productivity in the previous 3 months involving work, school, household work, and family, social, and leisure activities. Patients scoring from 0 to 5 (days) are considered to have grade I disability level, a score of 6 to 10 indicates grade II, a score of 11 to 20 indicates grade III, and a score greater than 20 indicates grade IV. Two nonscoring questions provided additional information relating to the number of headache days and headache severity over the previous 3 months.

Statistical Analysis.—Changes in MIDAS score, number of headache days, and headache severity from baseline to the end of the treatment period were analyzed for statistical significance using the Wilcoxon method.

RESULTS

The patient population in the present study included 10 female and 2 male patients aged 22 to 58 years (mean age ± SD: 41.1 ± 13.2). Patients exhibited a broad range of clinical presentations: headaches were variously described as left or right frontal, bilateral frontal, bilateral frontal/temporal, bilateral frontal/top, left temporal, left side, right parietal, or diffuse; age of first onset varied from 6 to 45 years (mean 19.5 ± 12.3); frequency varied from 2 to 30 per month (mean 9.8 ± 7.8); and duration varied from 1 to 3 days, although 1 patient reported headaches lasting as long as 7 days. In spite of no complete relief of headache, 8 patients continued taking 1, 3 patients taking 2, and 1 patient taking 3 prophylactic medications.

Of the 12 patients who were enrolled in the study, 11 successfully completed the 3-month treatment period and were included for analysis. One patient discontinued treatment on day 11 after reporting no change in headache frequency and was not considered in the analysis. Eleven patients reported no adverse events throughout the study.

At baseline, 8 of 11 patients had grade IV disability level and 3 had grade III disability level on the MIDAS scale. Following 3 months of therapy with the pine bark extract and vitamin antioxidant formulation, 3 patients remained at grade IV, 2 grade IV patients were re-graded to grade III, and 6 grade lll or lV patients were re-graded to grade I. Of the 3 patients who continued to demonstrate grade IV disability level, 1 showed a reduction in MIDAS score and in headache severity. The other 2 grade IV patients showed no improvement in MIDAS score, number of headache days, or headache severity and were classed as nonresponders.

Table 1.— Effect of 3 Months' Antioxidant Supplementation Therapy With a Pine Bark Extract/Vitamin C/E Formulation on Migraine Disability Assessment (MIDAS) Score in 11 Patients

MIDAS Items	Baseline	3 Months	Reduction From Baseline
Days of work or school missed	42	21	21 (50.0%)
Days where productivity half or less	59	28	31 (52.5%)
Days household work not done	104	51	53 (51.0%)
Days household productivity half or less	103	49	54 (52.4%)
Days where social activities missed	42	24	18 (42.9%)
Total days of 5 MIDAS items	350	173	177 (50.6%)
All patients (n = 11)			
Mean	31.8	15.7	16.1* (50.6%)
95% CI	18.9 to 44.8	1.0 to 30.4	8.2 to 23.9
Responders only (n = 9)			
Mean	28.7	9.2	19.5* (67.9%)
95% CI	14.3 to 43.0	0 to 22.4	11.8 to 27.1

*Indicates a significant difference ($P < .005$) between baseline and 3 months.

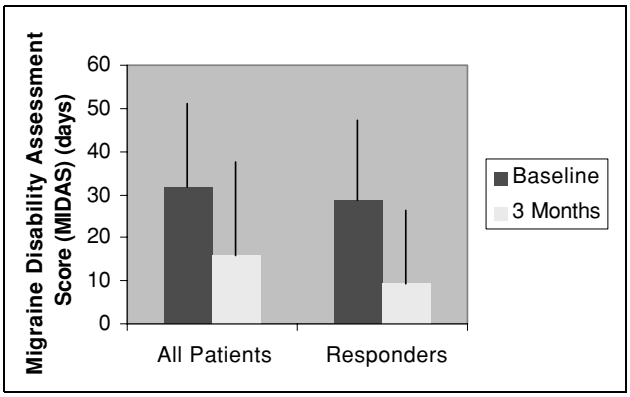

Fig 1.— Mean MIDAS score assessed over previous 3 months at baseline and following 3 months' therapy with antioxidant supplementation.

The 8 patients who demonstrated a reduction in MIDAS score and were re-graded to a lower grade also showed reductions in both number of headache days and the headache severity compared to the previous 3 months.

For the scoring component of the MIDAS assessment, total days of lost or limited activity due to migraine over a range of common activities in each disability item of 11 patients were counted and compared between baseline before therapy and 3 months after therapy, with the results summarized in Table 1.

Figure 1 shows that the mean MIDAS score for all patients was significantly reduced from 31.8 to 15.7 days ($P < .005$) while the mean MIDAS score for responders only decreased significantly from 28.7 to 9.2 days ($P < .005$) following 3 months of therapy. This was equivalent to a mean improvement of 50.6% and 67.9%, respectively, in patients' MIDAS scores.

At baseline, the mean number of headache days reported for the previous 3 months by all patients was 44.4 days while headache severity over the same period received a mean score of 7.5 (Table 2). Figures 2 and 3 show that following 3 months of therapy with the antioxidant formulation, the mean number of headache days reported by patients decreased significantly to 26.0 ($P < .005$) while headache severity also significantly decreased to a mean score of 5.5 ($P < .005$), equivalent to reductions of 41.4% and 26.7%, respectively.

When data from responders only were included for analysis, mean number of headache days and mean headache severity were significantly reduced from baseline by 56.0% and 33.3%, respectively ($P < .005$; Table 2).

COMMENTS

The finding in the present study that chronic migraine sufferers treated for 3 months with an antioxidant formulation of a flavonoid-rich pine bark extract plus vitamins C and E showed significant improvement in MIDAS score, headache frequency, and headache severity suggests that this antioxidant

Table 2.— Effect of 3 Months' Antioxidant Supplementation Therapy With a Pine Bark Extract/Vitamin C/E Formulation on Number of Headache Days and Headache Severity

		Baseline	3 Months	Reduction from Baseline
Number of headache days in previous 3 months (days)				
All Patients (n = 11)	Mean	44.4	26.0	18.4* (41.4%)
	95% CI	28.9 to 59.8	5.3 to 46.7	7.7 to 29.0
Responders only (n = 9)	Mean	40.2	17.7	22.5* (56.0%)
	95% CI	25.4 to 55.0	0 to 36.4	11.5 to 33.6
Severity of headaches over previous 3 months (symptom score, 0 to 10)				
All Patients (n = 11)	Mean	7.5	5.5	2.0* (26.7%)
	95% CI	6.7 to 8.4	4.1 to 7.0	0.9 to 3.1
Responders only (n = 9)	Mean	7.2	4.8	2.4* (33.3%)
	95% CI	6.5 to 8.0	3.6 to 5.9	1.4 to 3.5

*Indicates a significant difference ($P < .005$) between baseline and 3 months.

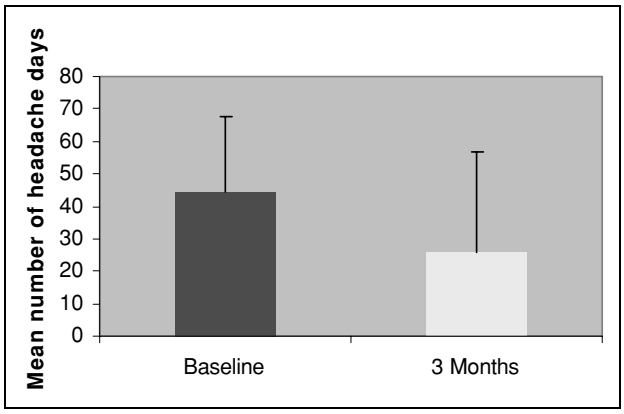

Fig 2.— Mean number of headache days over previous 3 months at baseline and following 3 months' therapy with antioxidant supplementation (all patients).

supplementation may mitigate some as yet unknown mechanisms involved in a migraine attack.

The antioxidant mixture used in this study is a potent, broad-spectrum, flavonoid-based supplement with vitamins C and E. It is well recognized that flavonoids are potent antioxidants and free radical scavengers. The substantial effect on migraine found in this study supports other evidence that free radicals may play an important role in the pathogenesis of migraine.[15-18]

Current studies demonstrate that free radicals, reactive oxygen species, and reactive nitrogen species are produced as by-products of normal cellular metabolism. When levels of these pro-oxidants exceed antioxidant capacity, oxidative stress can occur.[25] Increased oxidative stress within the cell typically regulates nuclear factor-kappa B (NF-κB).[25-27] NF-κB must be translocated from the cytoplasm to the nucleus to induce gene transcription.[28] This transcription factor plays a pivotal role in the expression of genes involved in inflammation. The expression of these and probably other proinflammatory proteins leads to increased blood vessel permeability, tissue edema, and pain sensitization, providing in part the molecular and functional mechanisms for migraine pathogenesis in the dura mater.[29]

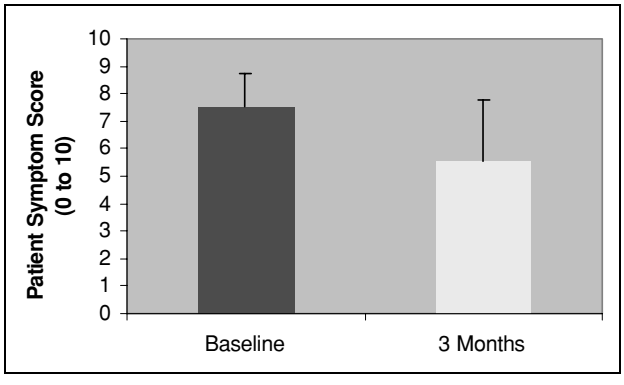

Fig 3.— Mean symptom score for headache severity over previous 3 months at baseline and following 3 months' therapy with antioxidant supplementation (all patients).

Antioxidant supplementation may protect cells from oxidative stress and reduce headache frequency and severity. However, antioxidative mechanism is one possible explanation since the pine bark extract may have other, eg, analgesic properties as well. This is a potentially important finding as all patients had failed other pharmacologic therapies and therefore represented a challenging treatment group. In conclusion, the substantial effect shown by the antioxidant formulation in the present study in lessening the impact of migraine on patients' daily activities warrants further investigation.

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