Efficacy of Pinus Radiata Bark Extract and Vitamin C Combination Product as a Prophylactic Therapy for Recalcitrant Migraine and Long-term Results

Sirichai Chayasirisobhon

Abstract-

Purpose: This was the open-label study to evaluate the potential benefit of Pinus radiata bark extract and vitamin C as a treatment for migraine.

Methods: Fifty outpatients with chronic migraine refractory to at least two prophylactic medications were treated with an antioxidant formulation of 1200 mg Pinus radiata bark extract and 150 mg vitamin C daily for 3 months. Patients completed migraine disability assessment (MIDAS) questionnaires at the beginning and end of the study to assess migraine impact on work, school, domestic and social activities over the three months prior to enrollment and the three month treatment period. Patients continued existing pharmacologic medications during the study. Patients who were responders were assessed for migraine impact using MIDAS questionnaires every 3 months for 12 months.

Results: Twenty nine patients (58%) showed improvement in MIDAS score, number of headache days and headache severity score over the 3 months of treatment. Mean MIDAS score significantly improved from 30.3 days at baseline to 14.4 days (p < 0.0001); mean number of headache days significantly reduced from 47.9 days at baseline to 25.9 days (p < 0.0001), and mean headache severity reduced from 8.1 out of 10 to 5.6 (p < 0.0001) after 3 months therapy. The responders who continuously took Pinus radiata bark extract and vitamin C combination for 12 months experienced ongoing migraine relief with more than 50% reduction of frequency and severity of headaches.

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.

Key Words: antioxidant, migraine, migraine disability assessment, pinus radiata bark extract

INTRODUCTION

There is a wide variety of therapeutic approaches both pharmacologic and non-pharmacologic for the migraine sufferer. The management of migraine can be divided into abortive and preventive therapies. Abortive treatments of migraine include non-steroidal anti-inflammatory drugs (NSAIDS), triptans, etc. along with...
non-pharmacological approaches such as sleep in a quiet
and dark room, and placing an ice pack on the head\(^1\)\(^2\).

The major classes of the medications for migraine
prevention are beta-blocker, calcium channel blockers,
tricyclic antidepressants, anticonvulsants and NSAIDS.
There are multiple mechanisms of actions on which the
preventive agents act. Beta-blockers are thought to inter-
act with 5-hydroxytryptamine (5-HT) or serotonin recep-
tors and cross modulation of the serotonin system\(^3\).
Calcium channel blockers block intracellular calcium
entry and cellular depolarization\(^4\)\(^5\). Tricyclic antidepres-
sants block reuptake of 5-HT at central sites\(^6\)\(^7\). Few anti-
convulsants have been approved for migraine preven-
tion. Valproate is thought to alleviate migraine via stimu-
lation of gamma-aminobutyric acid (GABA) synthesis
and inhibition of GABA degradation\(^8\)\(^9\). Topiramate alle-
viates migraine by potentiating GABA inhibition, block-
ing voltage-sensitive sodium ion channels and antago-
nizing non-NMDA glutamate excitatory receptors\(^10\)\(^11\).
NSAIDs inhibit prostaglandin and leukotriene synthesis
and inhibit the neurogenic inflammation of migraine\(^12\)\(^13\).

A number of herbal medicinal products have demon-
strated efficacy in migraine prophylaxis. Fewerfew
(Tanacetum parthenium) is rich in sesquiterpene lacto-
es, principally parthenolide\(^14\)\(^17\). It has inhibitory
effects on platelet aggregation and release of serotonin
from blood platelets and polymorphonuclear leuko-
cytes\(^14\)\(^15\)\(^16\)\(^18\). Butterbur (Petasites hybridus root) was found
before effective in the prophylaxis of migraine\(^20\)\(^21\).
Butterbur likely acts through calcium channel regulation
and inhibition of peptide leukotriene biosynthesis, thus
influencing the inflammatory cascade associated with
migraine\(^22\)\(^23\)\(^24\).

The effects of consuming an antioxidant formulation
consisting of the same Pinus radiata bark extract (1200
mg daily), as used in the present study (commonly
known under the trade name Enzogenol\(^8\)), in combina-
tion with 600 mg vitamin C and 300 IU of vitamin E
daily had previously been investigated in a small number
of migraine patients\(^25\). This treatment had shown
promise with reduced MIDAS scores and reduced
headache frequency and severity. Vitamin C and vitamin
E are well established dietary antioxidants with widely
accepted health benefits. The Pinus radiata bark extract
is an aqueous polyphenolic extract that consists of
proanthocyanidins as the major components with
approximately 75-80%, other flavonoids, stilbenes and
phenolic acids including dihydroquercetin, catechin,
astringenin, and ferulic acid\(^26\)\(^27\)\(^28\). The Pinus radiata bark
extract has demonstrated potent in-vitro antioxidant
activity, and clinical trials have shown that the extract
can reduce indicators of oxidative stress in-vivo includ-
ing plasma protein-carbonyls and leukocyte DNA dam-
age\(^29\)\(^30\).

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\(^31\). The present Pinus radiata 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\(^20\). The pre-
sent study has investigated the potential benefits and
long term outcome of the Pinus radiata bark extract
(1200 mg daily) in combination with vitamin C at a
quarter the dose of the previous study (150 mg daily),
and without vitamin E in the treatment of migraine
headache.

**METHODS**

This was prospectively collected data analysis of
uncontrolled, open-label study of 3 months duration.
Inclusion criteria were a long-term history of regular
migraine attacks diagnosed according to International
Headache Society criteria\(^32\), and having failed to
respond to at least two prophylactic medications of beta-
blockers, antidepressants, or anticonvulsants given for an
adequate period of time at an adequate dose. Criteria for
exclusion were other kinds of headache, and headache
caused by structural lesion, as well as diagnosis of med-
ication overuse according to the International Headache
Society criteria of medication overuse\(^33\). In order to reli-
ably 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.
There were no changes in patient’s medications during the study and patients were instructed to keep taking their medications. Twenty-four patients were using one, nine received two, and one patient was taking three prophylactic medications. Sixteen patients were using abortive therapy.

Every month for three months, patients received a supply of the antioxidant combination product containing 240 mg of Pinus radiata bark extract and 30 mg of vitamin C in each capsule and were instructed to take five capsules each morning in one dose. 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) questionnaires. This comprised five scoring questions to assess the number of days of lost or limited productivity in the previous three 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 migraine, a score of 6 to 10 indicates Grade II migraine, a score of 11 to 20 indicates Grade III migraine and a score greater than 20 indicates Grade IV migraine. Two non-scoring questions provided additional information relating to the number of headache days and headache severity over the previous 3 months.

The responders who continuously took Pinus radiata bark extract and vitamin C combination for 12 months were further assessed for migraine impact using MIDAS questionnaires.

This study design was approved by the ethics committees of Southern California Permanente Medical Group.

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

Fifty-five patients were enrolled in the study. One patient discontinued treatment on day 14 and two patients on day 28 after reporting no perceived change in headache frequency. One patient discontinued treatment on day 5 and another on day 7 after reporting abdominal discomfort. It was unclear whether these were treatment related events. Those five patients were not considered in the analysis. The 50 patients who successfully completed the 3-month treatment period and were included for analysis reported no adverse events throughout the study. Table 1 shows the demographic data of the population. There were 44 female and 6 male patients aged 14 to 68 years (mean age ± SD: 41.6 ± 13.4). Patients exhibited a broad range of clinical presentations: headaches were variously described as right or left frontal, bilateral frontal, right or left parietal, right or left temporal, bilateral temporal, bilateral frontal/temporal, right or left side of the head or diffuse; age of first onset

<table>
<thead>
<tr>
<th>Table 1. Demographic data of patient population</th>
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<tbody>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Mean age (year)</td>
</tr>
<tr>
<td>Age of onset (year)</td>
</tr>
<tr>
<td>Location of headache</td>
</tr>
<tr>
<td>Right side of head</td>
</tr>
<tr>
<td>Right parietal</td>
</tr>
<tr>
<td>Right temporal</td>
</tr>
<tr>
<td>Right parietal/temporal</td>
</tr>
<tr>
<td>Left side of head</td>
</tr>
<tr>
<td>Left frontal</td>
</tr>
<tr>
<td>Left parietal</td>
</tr>
<tr>
<td>Left temporal</td>
</tr>
<tr>
<td>Both sides of head</td>
</tr>
<tr>
<td>Both frontal</td>
</tr>
<tr>
<td>Both temporal</td>
</tr>
<tr>
<td>Both frontal/temporal</td>
</tr>
<tr>
<td>Headache with aura</td>
</tr>
<tr>
<td>Headache without aura</td>
</tr>
<tr>
<td>Duration of aura</td>
</tr>
<tr>
<td>Prophylactic therapy</td>
</tr>
<tr>
<td>One drug</td>
</tr>
<tr>
<td>Two drugs</td>
</tr>
<tr>
<td>Three drugs</td>
</tr>
<tr>
<td>Abortive therapy alone</td>
</tr>
</tbody>
</table>
varied from 6 to 57 years (mean 23.3±13.3); frequency
did not vary from 2 to 30 per month (mean 15.7±9.7); and
duration varied from 0.25 to 4 days (mean 1.4±0.8).

Twenty-nine patients (58.0%) demonstrated a reduct-
ion in MIDAS score, number of headache days and
headache severity over the previous 3 months. The mean
onset of headache relief was 24.8±18.0 days. The ear-
liest onset of headache relief was three days in one patient
and the longest onset of headache relief was 80 days.

At baseline, 29 of 50 patients had grade IV migraine,
13 had grade III migraine and 8 had grade II migraine on
the MIDAS scale. Following 3 months of therapy 13
patients remained at grade IV. One showed a reduction
in MIDAS score and in headache severity while 12
showed no improvement in MIDAS score, number of
headache days or headache severity and were classified
as non-responders. Three grade IV patients were re-grad-
ed to grade III, one grade IV was re-graded to grade II
and twelve grade IV patients were re-graded to grade I.
Two grade III patients remained grade III, one grade III
was re-graded to grade II and 10 were re-graded to grade
I. Four grade II patients remained at grade II and 4 were
re-graded to grade I.

For the scoring component of the MIDAS assess-
ment, total days of lost or limited activity due to
migraine over a range of common activities were count-
ed, with results summarized in Table 2.

The mean MIDAS score for all patients was signifi-
cantly reduced from 30.3 days to 14.4 days (p < 0.0001).
This was equivalent to a mean improvement of 52.3% in
patients’ MIDAS scores. (Figure 1)

At baseline the mean number of headache days
reported for the previous 3 months by all patients was
47.9 days whilst headache severity over the same period
received a mean score of 8.1 (Table 3). Figures 2 and 3
show that following 3 months of therapy with the antioxi-
dant formulation, the mean number of headache days
reported by patients decreased significantly to 25.9 (p <
0.0001) whilst headache severity also significantly
decreased to a mean score of 5.6 (p < 0.0001), equiva-

tent to reductions of 45.9% and 30.9%, respectively.

When data from responders only were included for
analysis (Figure 1, 2 and 3), mean MIDAS score for

![Figure 1. Mean MIDAS score assessed over previous 3 months at
baseline and following 3 months’ therapy with antioxidant
supplementation.](image1)

![Figure 2. Mean numbers of headache days over previous 3 months
at baseline and following 3 month’s therapy with antioxi-
dant supplementation.](image2)

![Figure 3. Mean symptom score for headache severity over previous
3 months at baseline and following 3 month’s therapy with antioxi-
dant supplementation.](image3)
Table 2. Effect of 3 months’ antioxidant supplementation therapy with a pine bark extract/vitamin C formulation on Migraine Disability Assessment (MIDAS) score.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Months</th>
<th>Reduction from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of work or school missed</td>
<td>168</td>
<td>50</td>
<td>118 (70.2%)</td>
</tr>
<tr>
<td>Days where productivity half or less</td>
<td>460</td>
<td>158</td>
<td>302 (65.7%)</td>
</tr>
<tr>
<td>Days household work not done</td>
<td>296</td>
<td>207</td>
<td>89 (30.1%)</td>
</tr>
<tr>
<td>Days household productivity half or less</td>
<td>489</td>
<td>244</td>
<td>267 (50.1%)</td>
</tr>
<tr>
<td>Days where social activities missed</td>
<td>104</td>
<td>62</td>
<td>42 (40.4%)</td>
</tr>
<tr>
<td>Total days (all patients)</td>
<td>1517</td>
<td>721</td>
<td>796 (52.5%)</td>
</tr>
<tr>
<td>MIDAS Score (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (mean)</td>
<td>30.3</td>
<td>14.4</td>
<td>15.9* (52.5%)</td>
</tr>
<tr>
<td>Responders (mean)</td>
<td>28.3</td>
<td>2.5</td>
<td>25.8* (91.2%)</td>
</tr>
</tbody>
</table>

* Indicates a significant difference (p<0.0001) between baseline and 3 months.

Table 3. Effect of 3 months’ antioxidant supplementation therapy with a Pinus radiata bark extract/vitamin C formulation on number of headache days and headache severity.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Months</th>
<th>Reduction from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of headache days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (50 patients)</td>
<td>47.9</td>
<td>25.9</td>
<td>22.0* (45.9%)</td>
</tr>
<tr>
<td>Responders (29 patients)</td>
<td>48.4</td>
<td>8.7</td>
<td>39.7* (82.0%)</td>
</tr>
<tr>
<td>Severity of headache (symptom score, 0 to 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients (50 patients)</td>
<td>8.1</td>
<td>5.6</td>
<td>2.5* (30.9%)</td>
</tr>
<tr>
<td>Responders (29 patients)</td>
<td>8.0</td>
<td>3.9</td>
<td>4.1* (51.3%)</td>
</tr>
</tbody>
</table>

* Indicates a significant difference (p<0.0001) between baseline and 3 months.

Table 4. Comparison of MIDAS score, frequency of headache in 3 months and mean severity of headache score of 16 responders at baseline, 3rd month, 6th month, 9th month and 12th month.

<table>
<thead>
<tr>
<th>Patient</th>
<th>MIDAS score</th>
<th>Frequency per 3 month</th>
<th>mean severity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>15/0/0/0/0*</td>
<td>15/4/3/3/1</td>
<td>8/5/2/1/1</td>
</tr>
<tr>
<td>2.</td>
<td>12/1/0/0/0</td>
<td>27/6/2/0/0</td>
<td>8/2/7/1/0</td>
</tr>
<tr>
<td>3.</td>
<td>27/0/0/0/0</td>
<td>15/1/1/0/0</td>
<td>8/7/2/0/0</td>
</tr>
<tr>
<td>4.</td>
<td>48/24/0/0/0</td>
<td>90/4/2/1/1</td>
<td>9/8/2/2/2</td>
</tr>
<tr>
<td>5.</td>
<td>18/0/0/0/0</td>
<td>36/6/1/1/1</td>
<td>7/3/2/2/2</td>
</tr>
<tr>
<td>6.</td>
<td>12/0/0/0/0</td>
<td>12/1/0/0/0</td>
<td>7/2/0/0/0</td>
</tr>
<tr>
<td>7.</td>
<td>13/0/0/0/0</td>
<td>9/1/0/0/0</td>
<td>9/5/0/0/0</td>
</tr>
<tr>
<td>8.</td>
<td>30/0/0/0/0</td>
<td>90/1/1/1/1</td>
<td>8/5/2/2/2</td>
</tr>
<tr>
<td>9.</td>
<td>84/18/3/4/3</td>
<td>90/18/6/11/5</td>
<td>7/3/3/3/3</td>
</tr>
<tr>
<td>10.</td>
<td>21/2/3/3/3</td>
<td>89/14/5/4/4</td>
<td>8/2/3/4/4</td>
</tr>
<tr>
<td>11.</td>
<td>35/0/3/4/2</td>
<td>89/3/5/4/5</td>
<td>7/2/3/3/3</td>
</tr>
<tr>
<td>12.</td>
<td>9/0/1/1/1</td>
<td>88/12/10/9/11</td>
<td>7/3/4/3/3</td>
</tr>
<tr>
<td>13.</td>
<td>12/0/1/1/1</td>
<td>62/5/7/4/4</td>
<td>10/7/4/4/4</td>
</tr>
<tr>
<td>14.</td>
<td>12/1/1/1/1</td>
<td>12/1/10/12/11</td>
<td>6.5/3/2/2/2</td>
</tr>
<tr>
<td>15.</td>
<td>48/0/0/0/0</td>
<td>60/18/0/0/0</td>
<td>6/2/0/0/0</td>
</tr>
<tr>
<td>16.</td>
<td>24/0/0/0/0</td>
<td>45/14/0/0/0</td>
<td>8/3/0/0/0</td>
</tr>
</tbody>
</table>

*N/N/N/N/N=baseline/3rd month/6th month/9th month/12th month
responders decreased significantly from 28.3 days to 2.5 days ($p < 0.0001$) following 3 months of therapy. This was equivalent to a mean improvement of 91.2% in patients’ MIDAS scores. Mean number of headache days and mean headache severity was significantly reduced from baseline by 82.0% and 51.3% respectively ($p < 0.0001$; Table 3). Lastly, in the responder group, the mean number of headache in 1st, 2nd and 3rd month of therapy with the antioxidant formulation was $6.9 \pm 5.9$, $2.1 \pm 4.4$ and $1.0 \pm 1.9$, respectively. This suggested that the frequency of headache decreased progressively over the 3 months of therapy.

Of 29 patients who were responders, thirteen patients, whose headaches had subsided, decided not to participate in long-term study. They were able to come off the prophylactic medications and required only abortive therapy for mild headaches. Two of these patients had the recurrence of major headache (one patient at 6th month and another at 9th month). One responded to re-instating of Pinus radiata bark extract, while the other continued to have headaches but at lesser severity when compared to baseline. The remaining 16 patients continued the study supplement for 12 months and experienced ongoing migraine relief with more than 50% reduction in frequency and severity of headaches. (Table 4)

**DISCUSSION**

Treatment and management of migraine is complicated by 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 attacks35. Recent evidence implicates oxidative damage caused by free radicals in the brain as playing a role in the pathogenesis of migraine headache. The most convincing evidence for free radical activity comes from nitric oxide (NO), which is a potent vasodilator and is an important biochemical in the trigeminal-vascular peripheral mechanism of migraine headache35,36. Nitric oxide is released during cortical spreading depression across the cortex resulting in releasing calcitonin gene-related peptide (CGRP) from certain neurons, potentially producing vasodilatation and headache. NO is formed in the post-synaptic neuron following activation of N-methyl-D-aspartate (NMDA) receptors. Furthermore, studies have shown platelet levels of nitric oxide, as well as nitric oxide metabolites such as nitrate/nitrite, are increased in migraineurs and rise further during attacks37,38. Therefore, free radical scavenging antioxidants may provide a potential molecular basis for prophylactic anti-migraine therapy by neutralizing nitric oxide overproduction and possibly preventing formation of highly toxic peroxynitrite.

Other free radicals, such as reactive oxygen species (ROS) that are normal by-products of cellular electron transfer reactions, ordinary metabolic processes and immune system responses are important in inflammation and may play a role in nociceptor activation of migraine attack39.

Other observations using PET have demonstrated that periaqueductal gray (PAG) matter is essential in migraine pathophysiology40. Dysfunction of brainstem areas involved in the modulation of cranio-vascular afferent fiber most likely result in migraine.41 Subsequent studies of iron homeostasis in the PAG matter of migraine patients were performed. Highly elevated iron levels in PAG matter were observed in patients with either episodic migraine or chronic daily headache, with the highest tissue iron levels measured in those patients who had prolonged illness with severe and frequent episodic migraine or chronic daily headache. Repeated episodes of hyperoxia of brainstem structures activated during migraine attacks could render these areas at risk for iron-catalyzed free radical damage42. When levels of these free radicals that are pro-oxidants exceed antioxidant capacity, oxidative stress can occur43. Increased oxidative stress within the cell typically regulates nuclear factor-kappa B (NF-kB)44,45. NF-kB must be translocated from the cytoplasm to the nucleus to induce gene transcription45. This transcription factor plays a pivotal role in the expression of genes involved in inflammation. The expression of these and probably other pro-inflammatory proteins leads to increased blood vessel permeability, tissue edema and pain sensitization,
providing in part the molecular and functional mechanisms for migraine pathogenesis in dura mater(47). The above evidence indicates that free radicals may play an important role in the pathogenesis of migraine(35-38). The earlier study of Pinus radiata bark extract plus vitamins C and E indicated potential efficacy in the treatment of migraine(25). The treatment used in the present study did not contain the vitamin E and only one-fourth the dose of vitamin C, demonstrating that vitamin E was not required and vitamin C at least partially redundant for the effects on migraine seen in these studies.

The findings of the present study continue to demonstrate that chronic migraine sufferers treated for 3 months with this antioxidant combination show significant improvement in MIDAS score, headache frequency and headache severity. The actual mechanisms by which the Pinus radiata bark extract plus vitamin C combination prevent migraine symptoms is not known. Anti-oxidation effects could be one possible explanation given that the Pinus radiata bark extract is a potent, broad-spectrum, flavonoid-based antioxidant that together with vitamin C can reduce overall oxidation levels in the body as previously shown in a randomized controlled study by Young et al(30) where significant reductions in plasma protein carbonyls were observed with a lower dose of the same antioxidant combination. Anti-inflammatory effects of the Pinus radiata bark extract have recently been demonstrated in an in-vitro model of atherosclerosis where the extract appeared to induce down-regulation of NF-κB-dependent signaling events involved in leukocyte transmigration across the endothelium(48).

The present Pinus radiata bark extract and vitamin C combination has shown the potential for cardiovascular and neurological benefits in different populations of generally healthy individuals including improved endothelial function, reduced plasma fibrinogen concentrations and reduced plasma viscosity and systolic blood pressure and improved cognitive functioning(26,30,49). It is concluded that Pinus radiata bark extract as an antioxidant supplementation may play a role in protecting the brain cells from reactive oxygen species. It may protect cells from oxidative stress and reduce headache frequency and severity.

This study offers a new agent to add to the armamentarium of migraine management, especially recalcitrant migraine. The Pinus radiata bark extract and vitamin C combination has the potential to benefit challenging group of patients who fail other treatment modalities including prophylactic pharmacotherapeutic agents. This combination supplement also shows a promise for long term efficacy in migraine prophylaxis. However, this being a small open label study, further clinical investigation into the efficacy of this treatment, including randomized controlled trials, is necessary to confirm the present findings.

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REFERENCES