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Feverfew (*Tanacetum parthenium)* as a Prophylactic Treatment for Migraine: A Double-blind Placebo-controlled Study

D. Palevitch,[1]* G. Earon[2] and R. Carasso[3]

[1] Unit of Medicinal and Aromatic Plants, Newe Yaár Research Center, P.O. Box 1021, Ramat Yishay, 30095, Israel
[2] Private Clinic, 125 Rothschild Blvd., Tel Aviv, Israel
[3] Outpatient Pain Clinic, Hillel Yaffe Hospital, Hadera, Israel

To assess the effectiveness of feverfew as a prophylactic therapy for migraine, a double-blind placebo controlled cross-over trial was conducted for a period of 4 months. Fifty seven patients who attended an outpatient pain clinic were selected at random and divided into two groups. Both groups were treated with feverfew in the preliminary phase (phase 1), which lasted 2 months. In the second and third phases, which continued for an additional 2 months, a double-blind placebo-controlled cross-over study was conducted.

The results showed that feverfew caused a significant reduction in pain intensity compared with the placebo treatment. Moreover, a profound reduction was recorded concerning the severity of the typical symptoms that are usually linked to migraine attacks, such as vomiting, nausea, sensitivity to noise and sensitivity to light. Transferring the feverfew-treated group to the placebo treatment resulted in an augmentation of the pain intensity as well as an increase in the severity of the linked symptoms. In contrast, shifting the placebo group to feverfew therapy resulted in a reduction of the pain intensity as well as in the severity of the linked symptoms.

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INTRODUCTION

The clinical management of patients with migraine remains unsatisfactory because benefit from even the most potent analgesic agents is limited (Peatfield, 1988). Thus, greater emphasis has been recently placed on the prevention of attacks rather than on ingesting analgesic drugs during the attacks. Herbal treatment including various plant species is recommended to prevent and treat headaches (Laurinaitis, 1995). The most known herbal remedy involves the fresh leaves and leaf infusion of feverfew (*Tanacetum parthenium* (L.) Schultz-Bip.), a member of the Compositae (Asteraceae) family.

The preparations of this plant have long been used as a self-medication in the prevention of migraine and other types of headaches, since the time of the famous Greek doctor Dioscorides (50 A.D.), through medieval times and up to the present modern phytomedicine. It is employed also in fever, regulation of menstruation, stomach and toothache, insect bites, arthritis and asthma (Berry, 1984). The history, botany, chemistry and pharmacognosy of feverfew are well reviewed (see Awang, 1993; Hobbs, 1989; Lette, 1992). Although the pharmacological activity of feverfew has been investigated extensively, the exact mechanism of action is not yet fully understood. Most reports on the chemistry of feverfew have been associated with the sesquiterpene lactones (Abad *et al*., 1995). Parthenolide is considered as the major lactone, being present in variable amounts up to 1.7% in the leaves and flowerheads of feverfew (Awang, 1993; Banthorpe *et al*., 1990; Heptinstall *et al*., 1992). Biological and physiological studies have revealed that the plant extracts exhibit inhibitory effects on platelet aggregation (Heptinstall *et al*., 1985), inhibition of eicosanoid biosynthesis (Pugh and Sambo, 1988), inhibition of platelet phospholipase A_2 (Makheja and Bailey, 1982), and release of 5-hydroxytryptamine (5-HT; serotonin) from blood platelets and from polymorphonuclear leukocytes (Heptinstall *et al*., 1985), all associated with the aetiology of migraine. Controlled clinical trials which encompassed feverfew leaves and extracts have been conducted in England (Johnson *et al*., 1985; Murphy *et al*., 1988). These studies demonstrated a significant level of feverfew effectiveness in preventing migraine. No major adverse effects in the long-term use of feverfew have been recorded. The prophylactic use of feverfew did not affect the frequency of chromosomal aberrations in the circulating peripheral lymphocytes of feverfew users (Anderson *et al*., 1988). The aim of the present clinical study was to evaluate the efficacy of Israeli grown feverfew as a prophylactic measure against migraine and other types of headaches.

MATERIALS AND METHODS

Plant material. Feverfew plants were cultivated at the Bet Dagan Experiment Station, in the coastal region of Israel. The seeds were purchased from Medigran Seed Company

* Correspondence to: D. Palevitch, Unit of Medicinal and Aromatic Plants, Newe Yaár Research Center, P.O. Box 1021, Ramat Yishay, 30095, Israel

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(The Netherlands). The leaves were harvested at the onset of flowering during May. After harvesting, the leaves were washed in water and soaked in a solution of 0.5% (v/v) sodium hypochloride for 10 min in order to reduce bacterial contamination. After rinsing in water, the leaves were dried in a stove heated to 45 °C and then stored at 4 °C until the onset of the clinical experiment. The parthenolide content of the dried leaves was 0.2% as determined by HPLC. Fifty mg of fine powdered leaves was packed in small gelatin capsules. Powdered dry leaves of parsley (*Petroselinum crispum*), were prepared in the same way, and served as the placebo control.

Patients. Fifty-seven patients (47 women and 10 men) with a median age of 38 (range 9 to 65 years old), who attended the hospital outpatient pain clinic were included in the study. The patients underwent medical examinations to evaluate the type of headache from which they suffered. They completed a questionnaire which included parameters such as number of years of suffering, frequency and duration of migraine attacks, pain intensity, sensitivity to a set of symptoms accompanying the migraine attacks including nausea, vomiting, and sensitivity to light and to noise. A numerical self-assessment pain scale was used, numbered from 0 to 10 where 0 represents no pain and 10 represents the most severe pain. The linked symptoms were estimated by the patients on a numerical analogue scale numbered from 0 to 4 (0 = none, 4 = severe). At the last meeting the patients were questioned about the following symptoms: pain intensity, pain frequency, pain symptoms and the severity of the accompanying symptoms.

Design. The present study was divided into three phases:
Phase 1 was designed as an open-labelled trial. The patients were divided at random into two groups (A and B). In this phase both groups received a daily dose of 100 mg feverfew (2 capsules) for 60 days.
Phases 2 and 3 were designed as a double-blind controlled randomized cross-over trial. Group A ($n=30$) continued to receive feverfew for an additional 30 days and then was shifted to the placebo treatment for 30 days (100 mg daily of ground parsley). Group B ($n=27$) received the first placebo treatment, for 30 days, and then was transferred to feverfew for the last 30 days. No intervention of washout periods between the experimental phases was involved in this trial.

Data analysis. For each patient the pain intensity was compared by paired *t* - test individually at the beginning of the study and then at the end of the open-labelled phase. A *t*-test was performed between group A and group B during phases 2 and 3. The symptoms linked with migraine attacks during the open-labelled trial were analysed according to the McNemar test (Jone and Kenward, 1989). According to this test only patients who responded to the treatment by showing improvement or deterioration in headache intensity were compared. The statistical analysis of the double-blind cross-over phases 2 and 3 was accomplished by the method of Mainland and Gart (Jone and Kenward, 1989), based on similar analogous principles to the McNemar test.

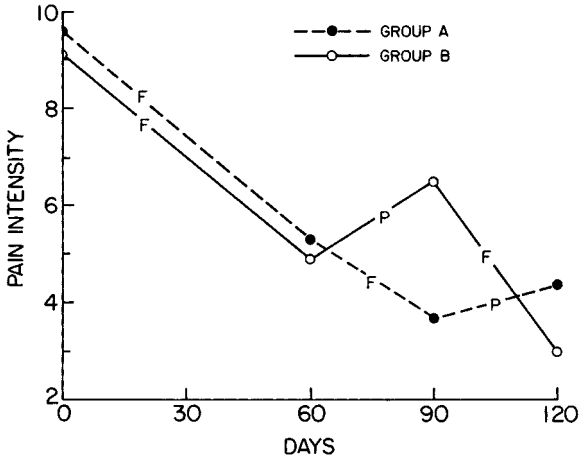

Figure 1. Effect of feverfew (F) vs placebo (P) on pain intensity in migraine patients (Pain recorded on an arbitrary scale from 0 = no pain to 10 = severe pain).

RESULTS

Pain intensity

The results of the open-labelled phase showed a notable reduction of the pain intensity (Fig. 1). After 60 days of feverfew treatment, the average pain intensity in the two groups (A and B; $n=57$) declined by 4.27 scale points (SE ± 0.38). The difference in pain intensity before and after the treatment with feverfew was highly significant ($p<0.001$). In the second phase when the double-blind design was implemented, the pain intensity of patients belonging to group A who received feverfew, decreased by 1.54 scale points (SE ± 0.66), whereas in the placebo group (B), an elevation of 1.55 scale points (SE ± 0.87) was recorded. The statistical difference between the two groups was significant ($p<0.01$). Similar results were achieved when the crossover procedure between the two groups took place (phase 3). The pain intensity of group B, which received the feverfew, diminished by 3.95 scale points (SE ± 1.08), whereas that intensity of the placebo group (A) was elevated by 1.36 scale points (SE ± 1.12), (Fig. 1).

Accompanying symptoms

In the open-labelled phase, a considerable lessening in the various symptoms such as vomiting, or sensitivity to light and noise was observed (Fig. 2). The differences were highly significant ($p<0.001$). The same magnitude was observed in comparing the two groups in the double-blind stage (Table 1). All the differences were highly significant ($p<0.001$) except for the sensitivity to noise in the first stage and after the crossover procedure ($p<0.017$ and $p<0.028$, respectively).

The results show clearly that feverfew brought about a significant reduction in intensity of migraine attacks among the chronic patients (43% suffered more than 10 attacks per month). The clinical improvement was achieved both during the open-label phase and the double-blind crossover trial. Shifting from the feverfew-treated group to the placebo group, or *vice versa*, resulted in an apparent augmentation or suppression of pain intensity (Fig. 1). A profound effect of the treatment with feverfew was

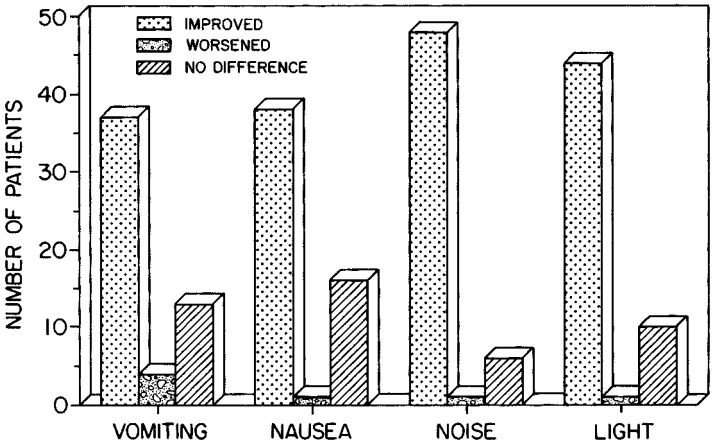

Figure 2. Effect of feverfew on symptoms associated with migraine.

demonstrated with the accompanying symptoms typical to migraine, such as nausea, inclination to vomit and sensitivity to light and noise (Fig. 2 and Table 1).

DISCUSSION

Chemoprevention of migraine by feverfew appears to be the most practical way to block completely, to slow down, or to ease migraine and headaches as well as to prevent the side effects associated with the common drug practices. A plethora of ethnopharmacological (Berry, 1984), chemical (Awang *et al*., 1991; Banthorpe *et al*., 1990), bioactivity (Heptinstall *et al*., 1992; Makheja and Bailey, 1982), metabolic (Anderson *et al*., 1988) and clinical (Johnson *et al*., 1985; Murphy *et al*., 1988), studies are providing convincing evidence that feverfew preparations are capable of providing a means of preventing migraine. Great emphasis has recently been placed on the prevention of attacks rather than on using analgesic drugs. Prophylaxis is based not only on greater clinical efficacy, but also on some aspects of the pathophysiology of migraine. Moreover, feverfew seems to be an attractive remedy also due to its slight or non toxic effect (Anderson *et al*., 1988).

Clinical studies showed that feverfew has therapeutic benefit. Its mode and site of action seem to be unique since it inhibits eicosanoid biosynthesis at the level of phospholipase A_2 (Makheja and Bailey, 1982) and not on the level of cyclooxygenase as do other nonsteroidal antiinflammatory drugs such as aspirin. Moreover, feverfew also exhibits its effect by inhibiting the secretory activity in the platelets and polymorphonuclear leukocytes (Heptinstall *et al*., 1985).

Johnson (1984), showed that among 300 migraine sufferers 70% claimed their migraine attacks were less frequent or less painful after consuming fresh leaves of feverfew for 2.5 years. Later, Johnson *et al*. (1985) presented the results of a placebo controlled clinical study with 17 patients who used feverfew as a self-treatment for several years prior to the onset of the trial. The attack frequency of the treated patients was reduced to 1.7 per month, which is similar to the attack rate when they had ingested fresh leaves of feverfew previously, during their self-treatment. The frequency of attacks in patients taking the placebo increased to 3.1 which is more than double the number of attacks reported during their self-treatment (1.2 attacks). The patients taking feverfew also suffered a far lower incidence of nausea and vomiting. Murphy *et al*. (1988) showed in a randomized double-blind placebo controlled trial that 59 patients who received feverfew for 4 months (of an 8 month trial), experienced fewer attacks and a reduction in the degree of vomiting. In contrast to the former trial in this study 42 of the 59 participants had never previously taken feverfew. When this group of non-users was considered separately, the reduction in number of attacks was greater.

It should be noted that our study is the first to be conducted among patients who had never taken feverfew before. The clear effect in reducing migraine pain intensity in phase 1 when all the patients received feverfew, can be attributed to this fact.

Genetic as well as environmental and cultivation conditions can cause variation in the sesquiterpene lactone content. A wide variation of the parthenolide content as well as the measurement of bioactivity (inhibition of serotonin release from blood platelets) was found in commercial products (Awang *et al*., 1991; Heptinstall *et al*., 1992). Since therapeutic efficacy has been demonstrated only with preparation of feverfew that contain parthenolide, it was suggested that manufacturers should standardize the active

Table 1. Effect of treatment (F) vs placebo (P) on symptoms accompanying migraine in the double-blind crossover (phases 2 and 3)

(Only data from patients who responded to the treatment are recorded).

Stage	Group	Treatment	Improved	Worsened	Odd ratio	*p*
Vomiting (% of patients)						
2	A	F	100	0	–	
	B	P	23.1	76.9	0.30	<0.001
3	B	F	100	0	–	
	A	P	20.0	80.0	0.25	<0.001
Nausea (%) of patients)						
2	A	F	72.2	27.8	2.60	
	B	P	6.3	92.7	0.07	<0.001
3	B	F	88.9	11.1	8.0	
	A	P	17.7	82.3	0.21	<0.001
Sensitivity to light (% of patients)						
2	A	F	75.0	25.0	3.00	
	B	P	12.5	87.5	0.14	<0.001
3	B	F	91.7	8.3	11.0	
	A	P	11.1	88.9	0.12	<0.001
Sensitivity to noise (% of patients)						
2	A	F	61.5	38.5	1.60	
	B	P	10.0	90.0	0.11	<0.017
3	B	F	100	0	–	
	A	P	37.5	62.5	0.6	<0.028

compounds and use quality control (Heptinstall *et al*., 1992).

The Canadian Protection Branch has granted DIN status to feverfew products standardized to a minimum level of 0.2% parthenolide, allowing the claim of effectiveness in prevention of migraine (Awang, 1993). This level was maintained in our trial. A higher quality of feverfew which has more than 0.5% parthenolide, is currently available in Israel (Galilee Herbal Remedy). It is considered worthwhile to use this high quality raw material in additional clinical studies.

The results of the present clinical trial provide convincing evidence that consuming a feverfew leaf preparation prophylactically, can ease profoundly the pain intensity and the prevalence of the typical symptoms associated with migraine attacks.

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