Acupuncture in the Prophylactic Treatment of Migraine Without Aura: A Comparison with Flunarizine

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Objectives.—In a randomized controlled trial extending over 6 months, we evaluated the effectiveness of acupuncture versus flunarizine in the prophylactic treatment of migraine without aura.

Methods.—One hundred sixty women with migraines were randomly assigned to acupuncture treatment (group A, n = 80) or to an oral therapy with flunarizine (group F, n = 80). In group A, acupuncture was carried out in weekly sessions for the first 2 months and then once a month for the next 4 months. The same acupoints were used at each treatment: LR3 *Taichong*, SP6 *Sanyinjiao*, ST36 *Zusanli*, CV12 *Zhongwan*, LI4 *Hegu*, PC6 *Neiguan*, GB20 *Fengchi*, GB14 *Yangbai*, EX-HN5 *Taiyang*, GV20 *Baihui.* In group F, 10 mg flunarizine were given daily for the first 2 months and then for 20 days per month for the next 4 months.

Results.—The frequency of attacks and use of symptomatic drugs significantly decreased during treatment in both groups. The number of attacks after 2 and 4 months of therapy was significantly lower in group A than in group F, and analgesic consumption was significantly lower in group A at 2 months of treatment. At 6 months no such differences existed between the two treatment groups. Pain intensity was significantly reduced only by acupuncture treatment. Side effects were significantly less frequent in group A.

Conclusions.—Acupuncture proved to be adequate for migraine prophylaxis. Relative to flunarizine, acupuncture treatment exhibited greater effectiveness in the first months of therapy and superior tolerability.

Key words: acupuncture, flunarizine, migraine, prophylaxis, randomized controlled trial

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Many uncontrolled studies have already reported encouraging results in the treatment of migraine by acupuncture. However, most of these observations suffer from a number of methodological shortcomings, and therefore the results should be treated with caution.[1] In recent years, other methodologically correct and controlled studies demonstrated that acupuncture is effective both in short term and in long term treatments.[2-6] Moreover, recent systematic reviews of published randomized controlled trials on acupuncture in headache prophylaxis have underlined the existing evidence that acupuncture has an effective role in the treatment of migraine,[7,8] but the evidence was not fully convincing, in particular for the small number of trials comparing acupuncture with other pharmacological treatments. Therefore we saw an urgent need for randomized controlled trials on large populations comparing acupuncture and drugs in headache prophylaxis.

Our aim was to determine, in a randomized controlled study, whether acupuncture proved to be effective in the prophylactic treatment of migraine without aura and to compare its efficacy with that obtained by a prophylactic course of flunarizine, one of the most commonly used drugs for migraine therapy.[9-11]

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METHODS

One hundred sixty women with migraines (mean age, 37.8 ± 9.8 years [range, 18 to 59]) were enrolled in the study. Criteria for the admission to the study were as follows: age ranging from 18 to 60 years, headache attacks showing the typical features of migraine without aura according to the International Headache Society criteria,[12] a minimum 2 years' history of migraine, more than 2 migraine crises per month in the last year, no past or present disease, no pregnancy or lactation, no inadequate contraception, and no previous treatment with acupuncture or other mind/body modalities. The use of a migraine prophylaxis was not allowed during the study, but no restriction was placed on analgesic intake.

According to a predetermined computer-made randomization list, the eligible patients were assigned, after a 2-month run-in period free of prophylactic therapy, to acupuncture treatment (group A; n = 80) or to an oral course with flunarizine (group F; n = 80). The patients had an equal probability of being assigned to either of the 2 treatment groups. Each patient was asked, before enrollment, to give an informed consent to participation in the study.

In group A acupuncture was carried out in weekly sessions for the first 2 months and then once a month for the next 4 months. To standardize the treatment scheme, consisting of local, adjacent, and distal points, we always punctured the following acupoints: LR3 Taichong, SP6 *Sanyinjiao*, ST36 *Zusanli*, CV12 *Zhongwan*, LI4 *Hegu*, PC6 *Neiguan*, GB20 *Fengchi*, GB14 *Yangbai*, EX-HN5 *Taiyang*, GV20 *Baihui* (Fig. 1). Unless for CV12 and GV20, located on the body median line, bilateral acupuncture was performed.

All points were punctured with 0.3-mm-diameter sterile disposable steel needles (length 52 mm) inserted to a depth of 10 to 30 mm and manipulated until the patient reported the characteristic irradiating sensation, said to indicate effective needling, which is commonly called *De Qi*.[13] Needles were inserted perpendicularly in all points (except GB14, Ex-HN5, and GV20, which were punctured horizontally).

For needle manipulation, the so-called even (intermediate) method was always used. After insertion, needles were manipulated by "raising and thrusting" and "twirling or rotating" methods. The depth of insertion during raising and thrusting of the needle was intermediate. During twirling the needle was rotated mainly to the right. After obtaining the needle sensation, the manipulation was stopped. The needles were left in situ for 20 minutes.

Acupuncture was always performed with the same needle manipulation technique by 3 of the authors (G. A., P. E. Q., G. T), who are experienced and qualified acupuncturists.

Acupoints were located as follows[14,15]:

- **LR3 *Taichong*:** on the dorsum of the foot, in the fossa distal to the junction of the first and second metatarsal bones, 2 inches proximal to the margin of the web of the toe;
- **SP6 *Sanyinjiao*:** 3 inches directly above the tip of the medial malleolus, in the fossa posterior to the medial margin of the tibia;
- **ST36 *Zusanli*:** in the fossa 1 fingerbreadth lateral to the anterior margin of the tibia and 3 inches inferior to the acupoint *Dubi* (ST 35), which is located at the lower border of the patella, in the depression lateral to the patellar ligament;
- **CV12 *Zhongwan*:** on the mid-abdominal line, at the midpoint between the xiphisternal joint and the umbilicus;

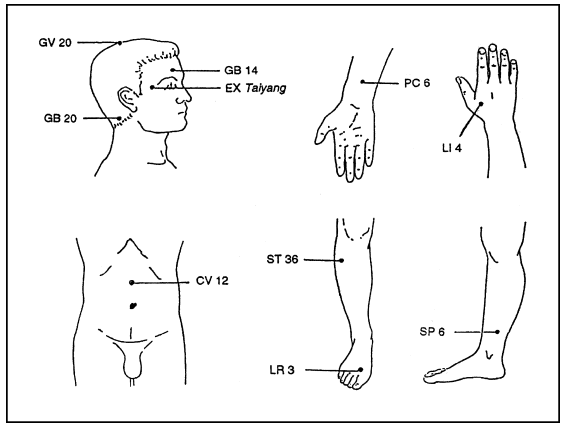

Fig 1.—Location of the acupoints used for migraine prophylaxis in this study. Acupuncture meridians are listed with the following abbreviations: GV, governor vessel; GB, gallbladder; EX, extra point; PC, pericardium; LI, large intestine; CV, conception vessel; ST, stomach; LR, liver; SP, spleen.

- **LI4 *Hegu*:** on the dorsum of the hand, between the first and second metacarpals, at the midpoint of the radial margin of the second metacarpal bone;
- **PC6 *Neiguan*:** on the palmar side of the forearm, 2 inches above the transverse crease of the wrist, and between the tendons of the flexor carpi radialis and palmaris longus muscles;
- **GB20 *Fengchi*:** at the posterior lateral aspect of the neck, in the fossa between the superior margins of the trapezius and sternocleidomastoid muscles;
- **GB14 *Yangbai*:** 1 inch above the midpoint of the eyebrow, directly above the pupil when looking straight ahead;
- **Ex-HN5 *Taiyang*:** at the point of intersection of the continuations of the eyebrow and the lower eyelid in the lateral direction, on the lateral border of the orbita;
- **GV20 *Baihui*:** at the middle of the vertex, on the line connecting the apexes of the two ears.

To avoid expectations, acupuncture was presented to the patients as a possible therapeutic approach to migraine prophylaxis, capable of controlling the genesis of pain, without any further explanation about its mechanisms of action.

In group F, 10 mg flunarizine was administered daily for the first 2 months and then 20 days per month for the next 4 months. This posological scheme, which entails brief interruptions of few days and is widely adopted in Italy, is formulated to take into account some of the features of the drug (eg, long half-life, tendency to accumulate) to minimize the side effects without reducing the prophylactic efficacy.[16]

The number of attacks (per month), intensity of pain, and the number of headache rescue medications were recorded in a headache diary in both groups. Their variations in respect to the run-in period (time 0 = T0) were calculated every 2 months (2 months = T1; 4 months = T2; 6 months = T3) as outcome measures. Decrease in the frequency of attacks was considered the main efficacy parameter. Migraine crises were recorded irrespective of their duration, and the following rules, as currently stated by the International Headache Society,[17] were applied for distinguishing an attack of long duration from 2 attacks or for distinguishing between attacks and recurrences: 1) a migraine attack that ended or was interrupted by sleep and then relapsed within 48 hours was recorded as a single attack, and 2) an attack treated successfully with medication but with relapse within 48 hours counted as 1 attack.

The severity of headache was evaluated by means of a 4-level semantic and behavioral scale: 0, no pain; 1, mild pain that does not inhibit routine activities; 2, moderate pain that limits routine activities without forcing the patient to bed; 3, severe pain that forces the patient to bed.

The analysis of the diary data was conducted by blind operators who did not know the group of each patient. Both patients in group A and F underwent a control visit by these operators every month.

Evaluation of the different parameters was carried out on a monthly basis and compared with the corresponding values during the run-in period (intragroup analysis) and to the corresponding values of the other treatment (intergroup analysis). All values given in text are reported as arithmetic means (± SEM).

Statistical evaluation was performed using an analysis of variance (ANOVA) for repeated measures; to localize the source of variance, a post-hoc Bonferroni *t* test was then applied. Moreover, to evaluate the difference between group F and group A, a *t* test for unpaired data was always performed for each level of the variable "time." In the case of proportions, a chi-square test was applied. Significance level was set at .05. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software program (version 8.0, SPSS, Inc., Chicago, Illinois).

Table 1.—Reasons for Withdrawal

Nature of Complaints	Number	Group
Drowsiness	3	F
Weight gain	3	F
Depression	1	F
Local pain	2	A
Change of abode	1	A

Table 2.—Demographics, Headache History, and Characteristics at Baseline of Patients Who Completed the Study

	Group A (n = 77)	Group F (n = 73)
Age, years	38.4 ± 9.7	37.2 ± 9.3
Blood pressure, mm Hg		
Systolic blood pressure	122.1 ± 11.3	120.0 ± 10.8
Diastolic blood pressure	75.4 ± 6.0	74.7 ± 7.0
Age at headache onset, years	17.9 ± 9.1	17.6 ± 8.8
Monthly frequency of attacks	6.4 ± 5.8	6.1 ± 5.3
Analgesic intake	9.7 ± 10.9	9.5 ± 11.2

Values are means ± SD.

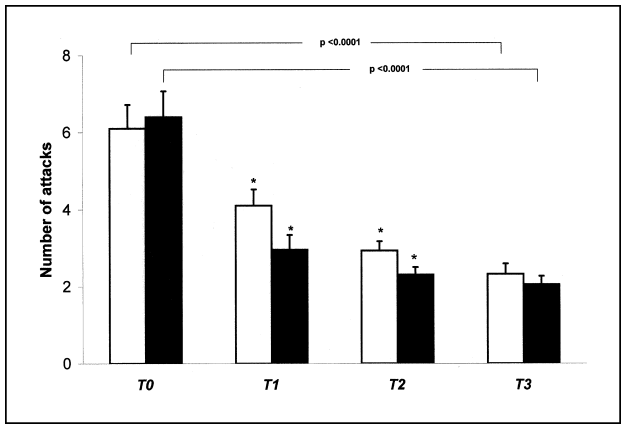

Fig 2.—Headache frequency during run-in period (T0) and after 2 months (T1), 4 months (T2), and 6 months (T3) of therapy in group A (black columns) and in group F (white columns). ANOVA for repeated measures: group A, $P<.0001$; group F, $P<.0001$. Bonferroni t test for intragroup analysis: group A: T0 vs. T1, T0 vs. T2, T0 vs. T3 = $P<.05$; T1 vs. T2, T1 vs. T3, T2 vs. T3 = n.s. ; group F: T0 vs. T1, T0 vs. T2, T0 vs. T3 = $P<.05$; T1 vs. T3 = $P<.05$; T1 vs. T2 = n.s. Unpaired t test for intergroup analysis at: T1 = $P<.05$; T2 = $P<.05$; T3 = n.s. *$\alpha<0.05$.

RESULTS

Ten patients, 7 from group F and 3 from group A, failed to complete the course of treatment. Table 1 reviews the reasons for the interruption of the trial given by the patients. The results are therefore based on the remaining 150 patients. The 2 groups remained homogeneous in terms of age, systolic and diastolic blood pressure, age at onset, and clinical characteristics of the disease (Table 2). During the run-in period, no significant difference was detectable from diary analysis between group A and group F for frequency and intensity of attacks or analgesic intake.

In group A there was a significant difference in headache activity among the various study times: the number of attacks, the intensity of pain, and the drug intake significantly decreased during acupuncture treatment. A similar trend was observed in group F for headache frequency and analgesic intake, but the drop in pain intensity was not significant in comparison with the basal evaluation.

As shown in Figure 2, the decrease in migraine frequency (main outcome measure of this study) was always significant in both groups during treatment (T1, T2, and T3) compared with the run-in period (ANOVA for repeated measures: $P<.0001$ either in group A [$F=23.66$] or in group F [$F=16.03$]). Statistical significance of this parameter was already reached after 2 months of therapy ($T1_A$ 2.95 ± 0.39 vs. $T0_A$ 6.40 ± 0.67 and $T1_F$ 4.10 ± 0.42 vs. $T0_F$ 6.10 ± 0.62; Bonferroni t test for both comparisons, $P<.05$), further improved at T_2 ($T2_A$ 2.30 ± 0.20 vs. $T0_A$ 6.40 ± 0.67 and $T2_F$ 2.93 ± 0.24 vs. $T0_F$ 6.10 ± 0.62; $P<.05$), and maintained at T_3 ($T3_A$ 2.05 ± 0.22 vs. $T0_A$ 6.40 ± 0.67 and $T3_F$ 2.32 ± 0.27 vs. $T0_F$ 6.10 ± 0.62; $P<.05$). In group F a further statistical significance was achieved comparing the results obtained after 2 and 6 months of therapy ($T3_F$ 2.32 ± 0.27 vs. $T1_F$ 4.10 ± 0.42; $P<.05$).

The number of migraine attacks was significantly lower in group A than in group F after 2 and 4 months of therapy ($T1_A$ 2.95 ± 0.39 vs. $T1_F$ 4.10 ± 0.42, 95% CI, 0.02 to 2.28; $T2_A$ 2.30 ± 0.20 vs. $T2_F$ 2.93 ± 0.24, 95% CI, 0.02 to 1.24; unpaired t test for both comparisons, $P<.05$). No difference in the number of migraine attacks was detectable between group A and F ($T3_A$ 2.05 ± 0.22 vs. $T3_F$ 2.32 ± 0.27; 95% CI, −0.41 to 0.95; P = n.s.) after 6 months of therapy.

As shown in Figure 3, the comparison of pain intensity before treatment and at the end of the therapeutic cycle showed a significant difference in group A ($\chi^2 = 14.59$ with 2 df; $P = .001$), whereas the difference in group F was not significant ($\chi^2 = 2.34$ with 2 df; $P = .310$). Moreover, 9.5% of patients (7/73) became headache free after the prophylactic course of

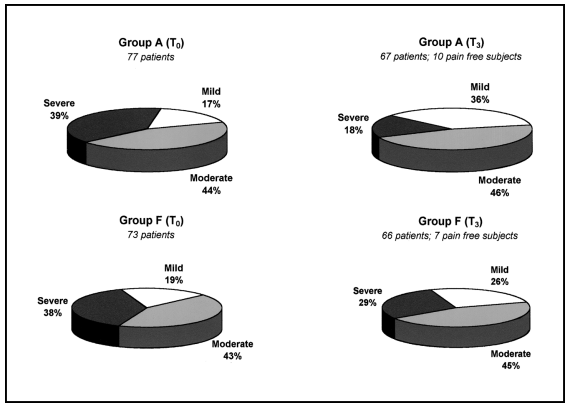

Fig 3.—Headache intensity. Frequency of the various class of pain intensity before (T_0) and at the end of (T_3) acupuncture treatment (top) and flunarizine treatment (bottom). In group A 10 patients became totally headache free, whereas in group F 7 patients achieved this condition.

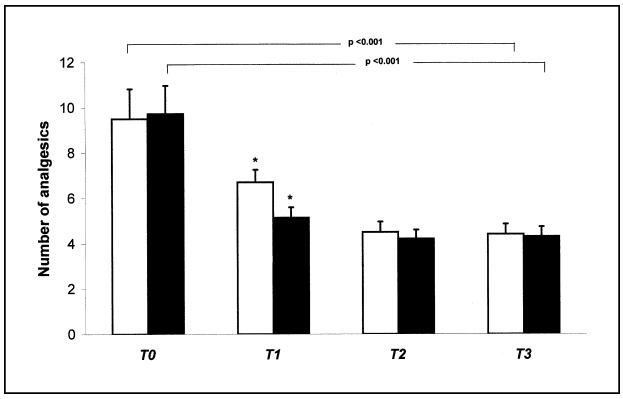

Fig 4.—Number of analgesic doses taken during run-in period (T0) and 2 months (T1), 4 months (T2), and 6 months (T3) of therapy in group A (black columns) and in group F (white columns). ANOVA for repeated measures: group A, $P<.001$; group F, $P<.001$. Bonferroni t test for intragroup analysis: group A: T0 vs. T1, T0 vs. T2, T0 vs. T3 = P<.05; T1 vs. T2, T1 vs. T3 = P<.05; T2 vs. T3 : n.s; group F: T0 vs. T1, T0 vs. T2, T0 vs. T3 = P<.05; T1 vs. T2, T1 vs. T3 = P<.05; T2 vs. T3 : n.s. Unpaired t test for intergroup analysis at T1 = P<.05, T2 = n.s., T3 = n.s. *α<.05.

flunarizine, compared with 12.9% of acupuncture-treated patients (10/77).

The amount of analgesics taken for migraine relief (Fig. 4) was progressively reduced by both therapies during the study period (ANOVA for repeated measures: $P<.001$ either in group A [$F = 13.00$] or in group F [$F = 9.32$]). Statistical significance of this parameter was already reached in group A after 2 months of therapy ($T1_A$ 5.13 ± 0.46 vs. $T0_A$ 9.72 ± 1.25; Bonferroni t test, $P<.05$), further improved at T_2 ($T2_A$ 4.20 ± 0.40 vs. $T0_A$ 9.72 ± 1.25; $P<.05$), and maintained at T_3 ($T3_A$ 4.30 ± 0.44 vs. $T0_A$ 9.72 ± 1.25; $P<.05$).

The intake of analgesics showed a different trend in group F. No significant difference was achieved at T1 ($T1_F$ 6.70 ± 0.56 vs. $T0_F$ 9.50 ± 1.32; Bonferroni t test, P = n.s.), but was reached at T2 ($T2_F$ 4.50 ± 0.46 vs. $T0_F$ 9.50 ± 1.32; $P<.05$) and maintained at T3 ($T3_F$ 4.40 ± 0.45 vs. $T0_F$ 9.50 ± 1.32; $P<.05$).

The number of analgesics used was significantly lower in group A than in group F at T1 ($T1_A$ 5.13 ± 0.46 vs. $T1_F$ 6.70 ± 0.56, 95% CI, 0.14 to 3.00; unpaired t test, $P<.05$). A greater number of subjects in group A (n = 18; 23.3%) than in group F (n = 11; 15.0%) completely stopped the use of rescue medications during the treatment.

Major side effects in group A were sedation after treatment (10%) and local pain (8%); the most frequently reported side effects in group F were drowsiness (35%), weight gain (22%), and depression (7%). The total number of patients reporting side effects was significantly lower in group A than in group F (10/77 vs. 29/73; $\chi^2 = 7.22$ with 1 df; $P = .007$).

COMMENTS

Our results demonstrate the efficacy of both acupuncture and flunarizine in the prophylactic treatment of migraine without aura. The number of headache attacks significantly decreased in group A and in group F. These findings are in agreement with those of Weinschütz et al[4] and Baischer[6] in their studies on acupuncture-treated patients; a significant reduction in the number of attacks was also noticed by Lenhard and Waite.[2] As for flunarizine prophylaxis, our data on the reduction of migraine frequency confirm those previously published.[9-11,18]

Acupuncture, when compared with flunarizine, proved to be more effective in reducing the number of migraine crises in the first 4 months of therapy. Acupuncture also significantly lowered the intensity of pain, which is in agreement with analogous findings of Vincent.[3] In group F no significant reduction of headache severity was registered; similarly, Louis[18] and Sorensen et al[19] found flunarizine superior to pla-

cebo in its effect on headache frequency but not on pain intensity.

In addition to the specific efficacy in pain treatment and the reduction of analgesic intake, acupuncture showed a minor incidence of side effects. The total number of patients complaining of side effects was significantly lower in group A, underlining the great tolerability of acupuncture. The percentage of patients that became totally pain free and completely stopped analgesic use was also greater in group A than in group F.

A peculiar characteristic of acupuncture needs to be underlined: especially in the first weeks of treatment, many patients reported the sensation of the imminence of a new attack, consisting of stitches and paresthesias, whose duration varied from a few seconds to some minutes. This sensation never transformed in a typical migraine crisis and never required drug intake.

Finally, a good clinical result was maintained by acupuncture in the last 4 months of therapy with a very low frequency of therapeutic sessions (1 per month). A further statistical consideration is worthy of mention. In some comparisons between group A and F, at various levels of the variable "time" along the treatment period significant differences were not present in our study. This fact does not automatically imply that acupuncture and flunarizine were equivalent in their effect. Quite often in past studies no significant difference was found between two drugs in trials for migraine prophylaxis, with some authors[20] concluding that the new treatment was as good as the established one. This statement could be accurate or not, depending on the so-called Type II error. Because the power of the present study was not calculated before starting it, it is correct to state that nothing can be concluded about the comparison between groups A and F when $\alpha > 0.05$. What we can affirm without doubt (because $\alpha < 0.05$) in the present study is that 1) acupuncture significantly reduces the frequency and the intensity of migraine attacks in comparison with the run-in period; 2) acupuncture is more effective than flunarizine in reducing the frequency of attacks after 2 and 4 months of treatment and pain intensity after 6 months of therapy; 3) acupuncture reduces progressively and significantly the amount of analgesics taken for migraine relief, and it shows a greater effectiveness than flunarizine after the first 2 months of treatment; and 4) acupuncture produces a significantly lower number of side effects than flunarizine.

A greater placebo effect could have occurred in group A, in which patients unavoidably received much more attention and hands-on treatments. Conversely, in this study acupuncture was applied in a reductive way. Traditional acupuncture has its own diagnostic system for headache that in some studies dictates the style and location of needle stimulation (this way of acupuncture performance was practically neglected in our study). To be as scientifically rigorous as possible, we always punctured the same acupoints in the same way in all patients during every therapeutic session (so-called formula acupuncture). This procedure could have limited the real possibilities of acupuncture. In fact, following the criteria of Traditional Chinese Medicine (TCM), it should have been applied in a more "personal" way and adjusted following the different changes in symptomatology of each patient. In any case, further scientific knowledge about the mechanisms of TCM's therapeutic effect is needed to confirm if real differences could be appreciated between personalized and formula acupuncture. At the moment no decisive scientific data are available in Western medical literature.

Finally, the number of acupoints stimulated, using our standardized scheme, was higher than that effectively required in most common cases, whereas the frequency of acupuncture sessions was less than ideal. Moreover, acupuncture was never performed in conjunction with other modalities (herbs, massage, etc.) as usually suggested by TCM. Even under these restrictive conditions, acupuncture treatment was effective, with few side effects; it should be considered more often as a primary choice for migraine prophylaxis.

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