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Research Submission

Traditional Acupuncture in Migraine: A Controlled, Randomized Study

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Objective.—To check the effectiveness of a true acupuncture treatment according to traditional Chinese medicine (TCM) in migraine without aura, comparing it to a standard mock acupuncture protocol, an accurate mock acupuncture healing ritual, and untreated controls.

Background.—Migraine prevalence is high and affects a relevant rate of adults in the productive phase of their life. Acupuncture has been increasingly advocated and used in Western countries for migraine treatment, but the evidence of its effectiveness still remains weak. A large variability of treatments is present in published studies and no acupoint selection according to TCM has been investigated so far; therefore, the low level of evidence of acupuncture effectiveness might partly depend on inappropriate treatment.

Design and Methods.—A prospective, randomized, controlled study was performed in 160 patients suffering from migraine without aura, assessed according to the ICD-10 classification. The patients were divided into the following 4 groups: (1) group TA, treated with true acupuncture (according to TCM) plus Rizatriptan; (2) group RMA, treated with ritualized mock acupuncture plus Rizatriptan; (3) group SMA, treated with standard mock acupuncture plus Rizatriptan; (4) group R, without prophylactic treatment with relief therapy only (Rizatriptan). The MIDAS Questionnaire was administered before treatment (T0), at 3 (T1) and 6 months (T2) from the beginning of treatment, and the MIDAS Index (MI) was calculated. Rizatriptan intake was also checked in all groups of patients at T0, T1, and T2. Group TA and RMA were evaluated according to TCM as well; then, the former was submitted to true acupuncture and the latter to mock acupuncture treatment resembling the same as TA. The statistical analysis was conducted with factorial ANOVA and multiple tests with a Bonferroni adjustment.

Results.—A total of 127 patients completed the study (33 dropouts): 32 belonged to group TA, 30 to group RMA, 31 to group SMA, and 34 to group R. Before treatment the MI (T_0) was moderate to severe with no significant intergroup differences. All groups underwent a decrease of MI at T_1 and T_2, with a significant group difference at both T_1 and T_2 compared to T_0 ($P < .0001$). Only TA provided a significant improvement at both T_1 and T_2 compared to R ($P < .0001$). RMA underwent a transient improvement of MI at T_1. The Rizatriptan intake paralleled the MI in all groups.

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Conflict of Interest: None

Conclusions.—TA was the only treatment able to provide a steady outcome improvement in comparison to the use of only Rizatriptan, while RMA showed a transient placebo effect at T1.

Key words: migraine, acupuncture, mock acupuncture, rizatriptan, MIDAS questionnaire, outcome

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Migraine prevalence is high and affects a high rate of adults in the productive phase of their life, causing significant disability and loss of daily activities, with relevant social and economic costs.[1–4] Furthermore, the majority of patients suffering from migraine report tension-type symptoms.[5–8] Despite the continuous progress in diagnosis and pharmacologic treatment of migraine, the outcome is still below the expectations: as a result, acupuncture and other non pharmacologic treatments have been increasingly advocated and used in western countries. In 1998 the NIH stated that acupuncture could be a useful adjunct treatment or an acceptable alternative in several disturbances, including headache,[9] while a recent study reported that some 12% of patients attending a neurology outpatient clinic had already tried acupuncture and 73% would be willing to do it.[10]

A growing number of systematic reviews indicates the potential value of acupuncture for the prevention of migraine,[11–15] but evidence still remains weak: the main source for weakness seems to be the large variability of study designs, preventing an accurate data analysis, thus leading the Cochrane review to conclude that there is an urgent need for well-planned, large-scale studies.

Recently, 3 studies with these features have been published,[16–18] 2 of them conclude that acupuncture provides persisting, relevant clinical benefits and health-related quality of life at a small additional cost, suggesting that an increase of acupuncture services in UK should be considered. The third study reports some effectiveness of both true and sham acupuncture at short-term follow-up (12 weeks), when compared to waiting list controls, but no difference between true and sham acupuncture; this gives rise to some concern about the specificity of acupoint selection, at least at a short-term outcome.

Acupuncture involves several specific problems related to research methods, including the problem of placebo (sham acupuncture is far from being a real placebo) and appropriate acupoint selection (see[19] as a review). As far as migraine is concerned, none of the published reviews properly addresses the problem of acupoint selection,[19,20] apart from the Cochrane review. A large variability of treatments was present in the studies quoted in the published systematic reviews, most of which seemed inappropriate according to traditional Chinese medicine (TCM).[20] As the acupoint selection is often skipped, the low level of evidence of acupuncture effectiveness might partly depend on inappropriate treatment, which might have a key role for efficacy (likewise the use of different drugs in Western medicine).

The aim of this controlled study is to check the effectiveness of a true acupuncture treatment according to TCM in migraine without aura, comparing it to a standard mock acupuncture protocol, an accurate mock acupuncture healing ritual, and untreated controls.

MATERIALS AND METHODS

A total of 160 patients affected by migraine without aura, with or without tension-type symptoms, were enrolled in the study; the frequency of migraine attacks was 3–8 per month and all the patients had previously received at least one prophylactic treatment for migraine with no improvement.

The diagnosis was performed according to the ICD-10 guide for headaches.[21] The exclusion criteria were: (1) onset of headache or acupuncture treatment less than 1-year before; (2) headache caused by other diseases.

All the patients were allowed to take Rizatriptan to treat the attacks, during the prophylactic treatment with acupuncture or placebo. Rizatriptan wafer was administered at a dose of 10 mg; a second dose was allowed after 2 hours if pain persisted.

The patients were stratified for sex and randomly divided into the following 4 groups of 40 patients each, using the random number generator in Microsoft

Excel: (1) group TA, treated with true acupuncture plus Rizatriptan; (2) group RMA, treated with ritualized mock acupuncture plus Rizatriptan; (3) group SMA, treated with standard mock acupuncture plus Rizatriptan; (4) group R, without prophylactic treatment with relief therapy only (Rizatriptan).

All the patients were required to fill in the Italian version of the MIDAS Questionnaire[22] for evaluating disability before treatment (T_0), at 3 (T_1) and 6 months (T_2) from the beginning of treatment; then, the MIDAS Index (MI) was calculated. The total number of Rizatriptan wafers taken in each 90-day period (T_1 and T_2) was recorded as well. A per-protocol analysis of results was conducted by the first author, who was not involved in the patients' treatment.

Acupuncture Treatment.—Since the Western picture of migraine does not clash with TCM classification of headache, all the patients were clinically evaluated according to the TCM syndrome differentiation and classified into the following, so called, internal or external syndromes:[23–26] (1) exogenous wind-cold attack; (2) exogenous wind-heat attack; (3) exogenous wind-dampness attack; (4) excess of liver yang; (5) obstruction of the middle jiao due to damp-phlegm; (6) deficiency of kidney essence; (7) stagnation of Qi and blood. Each type of syndrome was treated with a specific acupoint selection according to TCM (Table 1), as suggested by Liu Gongwan (Tianjin College of Traditional Chinese Medicine, personal communication); the acupoints were defined according to the WHO standard acupuncture nomenclature.

Twice a week, all the patients were submitted to 2 courses of 10 acupuncture applications each, with a 1-week rest between the 2 courses. Acupuncture was performed with single-use stainless steel filiform

Table 1.—Acupoint Selection in Migraine Without Aura, Classified in 7 subsets According to Traditional Chinese Medicine Classification of Headache

	Exogenous Syndromes			Internal Syndromes			
	Wind-cold	Wind-heat	Wind-Dampness	Excess of Liver Yang	Obstruction of Middle Jiao Due to Damp-phlegm	Deficiency of Kidney Essence	Stagnation of Qi and Blood
GB8	■			■			■
GB12						■	
GB20	■	■	■	■		■	■
GB38				■			
BL10						■	
BL12	■					■	
BL23						■	
BL60	■						
TE5		■					
ST8→GB8	■	■	■	■	■		
ST40			■		■		
SP6			■				■
SP9					■		
SP10							■
LR3				■			■
LR4				■			
KI3							
GV14		■					
GV23→GV20							
CV12			■		■		
EX-HN5	■	■	■		■		■
ASHlonGBCh				■	■		■
Method	↓	↓	↓	↓	↓	↑	↓

↓ = Reducing method; ↑ = Reinforcing method.

needles (according to Chinese manufacturing standards), 25 or 40 mm long and with a Ø of 0.30 mm.

In group TA, after the needle insertion and arrival of Qi, the required method of treatment was applied to each acupoint: the reducing method consisted of a 1 minute stimulation of the needle, obtained with a large rotation (amplitude >360°) at a rate of about 3 rotations/second. The reinforcing method was performed with a small rotation (amplitude <360°) for 1-minute at a rate of about one every 2 seconds. Stimulation was repeated 3 times at intervals of 5 minutes. The session lasted 30 minutes.

In patients belonging to group RMA, the acupuncture was apparently the same as in group TA, but the needles were not inserted. A small cylinder of foam (height and Ø = 1 cm) was applied to the skin by means of a double-adhesive plaster on each acupoint; then, needles with blunted tips were inserted into the cylinder, touching but not penetrating the skin. This allowed the patient to feel a superficial, light pricking-like sensation, thus simulating the needle insertion. A slight pressure was applied on the needle handle 3 times at 3 seconds intervals, in order to simulate the "arrival of Qi." The reducing or reinforcing methods were also simulated by rotating the needles within the foam cylinder. The protocol for diagnosis as well as acupoint selection according to TCM syndromes was the same as group TA, in order to check possible placebo effects related to the use of the TCM approach.

In patients belonging to group SMA only the Western approach was used for diagnosis and the following standard acupoint selection was used, with the same method of insertion used in group RMA: *Touwei* (ST8), *Xuanlu* (GB5), *Fengchi* (GB20), *Dazhui* (GV14), *Lieque* (LU7).

The statistical analysis was conducted by means of factorial ANOVA with groups and time (4 levels and 3 points) and multiple test with Bonferroni adjustment, for a significance level of $P = .05$, using program R (http://www.r-project.org). Since we did not know what effect size could be expected from the approach to TCM, we did not estimate the sample size based on a power calculation: enrolling 160 patients would have provided at least 30 patients in each group, taking into account possible dropouts.

RESULTS

A total of 127 out of 160 patients completed the study, while the remaining 33 dropped out: 32 belonged to group TA (8 dropouts), 30 to group RMA (10 dropouts), 31 to group SMA (9 dropouts), and 34 to group R (6 dropouts) (Fig. 1). All the groups were homogeneous as regards sex and age (Table 2). Patients' rating according to TCM (Table 3), an essential step to choose the appropriate treatment with classical acupuncture, showed that 53 cases (41.7%) belonged to external syndromes, while the so-called "excess of liver yang," including 49 cases (38.7%), was the most relevant single subset.

The MIDAS Index (MI) before treatment (T_0) was moderate to severe with no significant intergroup differences. Each group underwent a decrease of MI at T_1 and T_2, with a significant difference at both T_1 and T_2 compared to T_0 ($P < .0001$): the difference was significant for groups ($P < .0001$), time ($P < .0001$) and the interaction groups/time ($P < .001$) (Table 4).

TA showed a significant improvement of MI at both T_1 and T_2 compared to R, while RMA underwent a significant MI decrease at T_1 only (Table 4). The MI trend can be better observed in Figure 2: group TA showed a steady decrease of mean MI from 22.2 to about 2.2; group RMA underwent a transient decrease of MI from T0 to T1 and a subsequent increase from T_1 to T2, while SMA showed the same trend as group R. In short, TA proved to be the only treatment able to provide a steady outcome improvement in comparison to the use of Rizatriptan only, while RMA provided a transient significant placebo effect at T_1.

The interaction between time and groups showed a significant change of Rizatriptan intake from T_1 to T_2 ($P < .0001$) (Table 5). Only TA showed a significantly lower Rizatriptan intake at both T_1 and T_2 compared to R ($P < .0001$), as well as a significant decrease of intake from T_1 to T_2 ($P < .0001$). RMA showed a significantly lower Rizatriptan intake compared to R at T_1, but underwent an increase from T_1 to T_2, when it was within the range of SMA and R. The Rizatriptan intake paralleled the MI in all groups.

DISCUSSION

Headache is a major public health problem, due to its high prevalence. Despite the great progress in

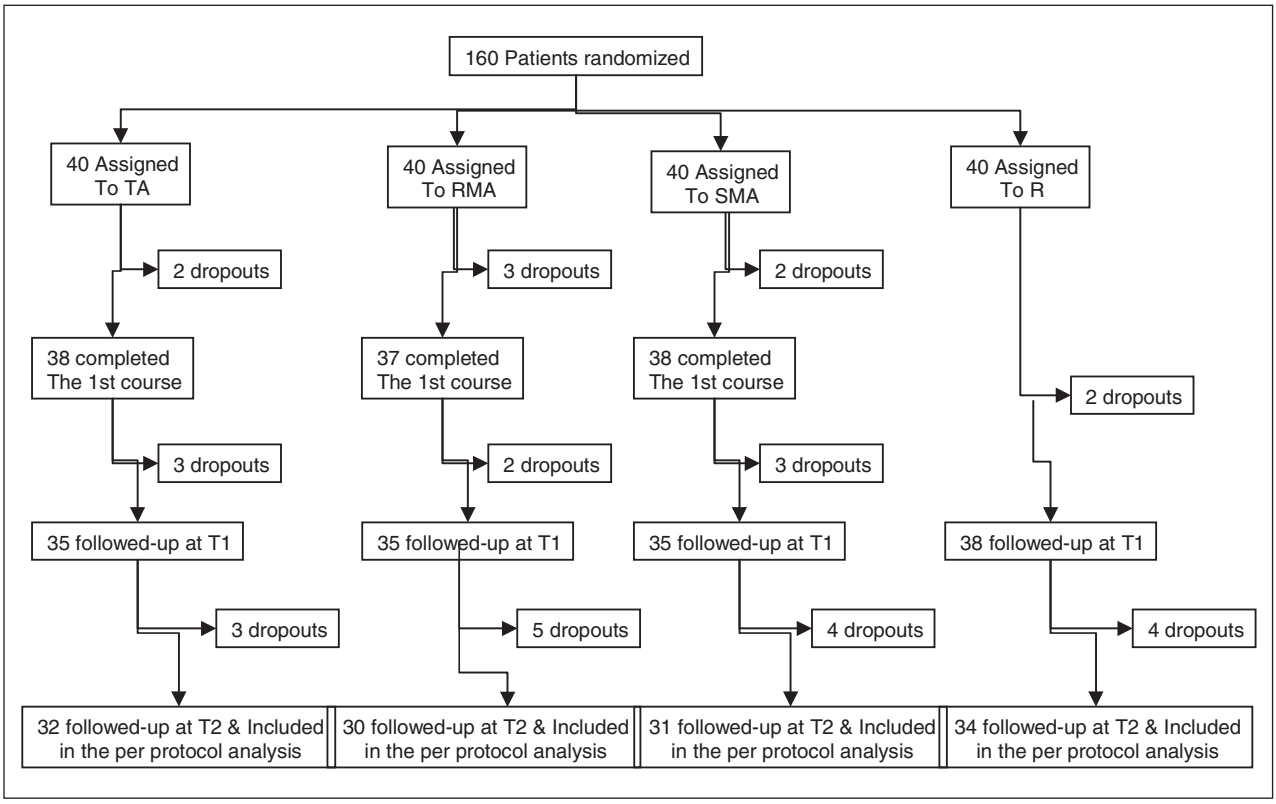

Fig 1.—Trial flow diagram.

pharmacologic treatment, many patients do not achieve optimal control, or do so only at the expense of unacceptable side-effects. As a result, an increasing use of behavioral as well as non-conventional therapies has occurred in the past 2 decades: acupuncture has been reported to be used by 19% of patients and is perceived as the most effective non-conventional treatment.[27] Similar data have been reported in migraine,[10] where about 12% of patients attending a neurology outpatient clinic reported that they had already tried acupuncture and 73% would be willing to try it. A recent review provides the rationale for traditional acupuncture indication in headache.[28]

Triptans have proved to be very effective drugs in the treatment of migraine attacks and have shown a class I evidence for effectiveness. Among triptans, Rizatriptan, a selective agonist of the 5-HT (1B/1D) receptors, has proved to be effective and well tolerated.[29] Rizatriptan has also been reported to improve the cost-effectiveness ratio, by decreasing migraine-related loss of work productivity.[30] Furthermore, Rizatriptan has been reported to be effective in migraine with tension-type symptoms as well.[7]

The MIDAS Questionnaire is the most extensively studied method for the assessment of headache-related disability[31–35] and has been validated in Italian patients.[22] The MIDAS score can reliably assess the impact of migraine and its changes may serve as an end point in assessing treatment efficacy.[36]

Given its proven mechanisms in analgesia,[28,37,38] acupuncture might provide long-lasting relief in

Table 2.—Age and Sex of 127 Patients With Migraine Without Aura

Group	Age (Mean ± SD)	Age Range	Sex
TA	35.2 ± 6.1	25-48	M/F 14/18
RMA	39.4 ± 6.4	25-50	M/F 14/16
SMA	35.4 ± 6.3	25-48	M/F 15/16
R	35.4 ± 6.9	25-54	M/F 16/18

Table 3.—Rating of Migraine in 127 Patients According to Traditional Chinese Medicine

Syndrome According to TCM	No. of Cases	%
Exogenous wind-cold attack	29	22.8
Exogenous wind-heat attack	16	12.6
Exogenous wind-dampness attack	8	6.3
Excess of Liver yang	49	38.7
Obstruction of Middle Jiao due to damp-phlegm	7	5.5
Deficit of Kidney essence	12	9.4
Stagnation of qi and blood	6	4.7

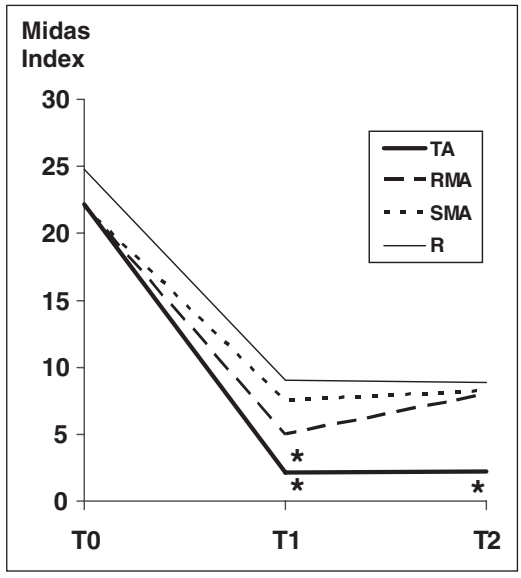

Fig 2.—Follow-up of migraine treated with acupuncture or placebo. At T1 both TA and RMA show a significant improvement of MIDAS Index compared to R; at T_2, TA only proves to be better than R (*$P < .0001$)

headache with a substantial lack of side effects. The wealth of available data strongly support the value of acupuncture for the prevention of headache,[11–15] but evidence still remains weak; a major source of weakness seems to be the bias introduced by variability of study designs and acupoint selection.

As far as acupoint selection is concerned, it is so variable in the published studies, as to prevent any evaluation of effectiveness.[19,20] Sometimes the authors do not even mention the acupoints they have chosen,[17,18] or only partially report them.[16] The problem of acupoint selection has been skipped in the mentioned systematic reviews, apart from the Cochrane review,[15] where one of the authors (G. Allais) checked the quality of acupuncture: he would have treated only 13 out of 26 studies (50%) in the same or in a similar way and 5 (19%) differently, while no judgment about acupuncture quality was possible with the remaining 8 (31%). Therefore, the appropriateness of acupoint selection remains an essential step for its validation: the studies providing no information on acupoint selection may keep their value in checking overall

Table 4.—MIDAS Index in Migraine Without Aura Before Treatment (T_0) and Follow-Up at 3 (T_1)and6Months(T_2)After Rizatriptan and Acupuncture or Placebo. All Groups are Significantly Different From T_0 at Both T_1 and T_2. TA has a Significantly Better Outcome than R Group at 3 and 6 Months, While RMA has a Significant Transient Effect at T_1 Only

Group	No. of Cases	To Mean ± SD	T1 Mean ± SD	T2 Mean ± SD	Multiple Test with Bonferroni Adjustment	
					T_1 vs T_0	T_2 vs T_1
TA	32	22.2 ± 6.0	2.1 ± 1.5*	2.2 ± 1.1**	t = 18.32; $P < .0001$	t = 18.52; $P < .0001$
RMA	30	22.1 ± 6.3	5.0 ± 1.5[§]	8.0 ± 1.5	t = 14.41; $P < .0001$	t = 11.89; $P < .0001$
SMA	31	22.0 ± 6.3	7.5 ± 3.3	8.2 ± 3.2	t = 11.36; $P < .0001$	t = 10.88; $P < .0001$
R	34	24.8 ± 6.6	9.0 ± 3.1	8.9 ± 3.1	t = 12.58; $P < .0001$	t = 12.72; $P < .0001$

Factorial ANOVA

Group: F = 28.74; $P < .0001$
Time: F = 658.03; $P < .0001$
Interaction group/time: F = 4.9; $P < .001$

*TA vs R at T_1: t = 11.53; $P < .0001$
**TA vs R at T_2: t = 11.79; $P < .0001$
[§]RMA vs R at T_1 = t = 6.63; < .0001

TA = true acupuncture plus Rizatriptan; RMA = ritualized mock acupuncture plus Rizatriptan; SMA = standard mock acupuncture plus Rizatriptan; R = Rizatriptan only.

Table 5.—Rizatriptan Intake in Migrainous Patients Treated With Rizatriptan and Acupuncture or Placebo at 3 (T_1)and6Months (T_2) After the Beginning of Treatment: Only Group TA Shows a Significant Decrease of Rizatriptan Intake From T_1 to T_2, While RMA Shows a Significant Rizatriptan Intake Decrease in Comparison to R at T_1 only, Followed by a Slight, Nonsignificant, Increase of Rizatriptan Intake From T_1 to T_2

Group	T1 No. of tabs Mean ± SD	T2 No. of Tabs Mean ± SD	Multiple Test With Bonferroni Adjustment T2 vs T1
TA	10.0 ± 5.0*	4.2 ± 1.5**	$t = 6.3$; $P < .0001$
RMA	14.4 ± 5.1§	17.0 ± 5.0	n.s.
SMA	17.2 ± 5.4	16.0 ± 5.0	n.s.
R	20.0 ± 5.1	18.5 ± 5.0	n.s.
Factorial ANOVA			
Group: F = 78.94; $P < .0001$			*TA vs R at T_1: $t = 8.02$; $P < .0001$
Time: F = 6.9; $P = .009$			**TA vs R at T_2: $t = 16.2$; $P < .0001$
Interaction groups/time: F = 8.1, $P < .0001$			§RMA vs R at T_1: $t = 4.4$; $P = .0004$

TA = true acupuncture plus Rizatriptan; RMA = ritualized mock acupuncture plus Rizatriptan; SMA = standard mock acupuncture plus Rizatriptan; R = Rizatriptan only.

acupuncture effectiveness (given its correct application), but can say nothing about the quality of treatment.

The aim of this study was to check the effects of traditional acupuncture in migraine, trying to provide reliable information on acupoint selection. This led us to face the TCM classification of syndromes, evaluating patients with both western medicine and TCM and selecting acupoints accordingly. It may seem inappropriate to discuss about TCM in a Western journal, however, we do believe that one cannot but face the paradigm of TCM and try to apply it in the process of acupuncture validation or falsification (in the epistemological sense of this term). To our knowledge, such an effort has never been made so far in Western journals.

As far as the TCM classification of headache is concerned, it is much less standardized than the Western one; furthermore, several symptoms other than pain are taken into account, while the features of pain are not well defined and quantified, as in the DC10 classification. As a result, some variability in symptoms and treatment can be found in different TCM texts:[23–26] in the attempt to find an effective treatment with a limited number of acupoints, we adopted the selection advised by Liu Gongwan (Tianjin College of Traditional Chinese Medicine, personal communication). Among TCM syndromes, the so-called "excess of Liver yang" and "deficiency of Kidney essence" seem to be the ones closer to Western migraine, since they imply throbbing pain, vomiting, and/or worsening with physical activity.[26] These 2 syndromes were found in nearly 50% of cases in our series, while the remaining ones probably reflected the coexistence of migraine and tension-type symptoms, indicating different acupuncture treatments.

In order to tell the difference between acupuncture and placebo effects, we compared true acupuncture to 3 different treatments: no acupuncture, standard mock acupuncture, and a ritualized mock acupuncture. The latter meant treating the patient according to TCM, exactly the same procedure used for true acupuncture. It enabled us to check the effects related to the different physician-patient relationship yielded by TCM. As TCM is more holistic and sensitive to all patient's sources of malaise (including coexisting symptoms other than pain), it might yield some positive results related to the patient's feeling of being better understood and cared for. Even though mock acupuncture has already proven to be a credible placebo (see[19] as a review), we modified the method for mock acupuncture in the attempt to improve its credibility. Touching the skin with a blunted needle tip made it possible to give the patient a light pricking-like sensation, while avoiding the problems related to sham acupuncture.

We did not administer a *post hoc* questionnaire and this may be a limit of the study; however, the positive result of RMA at T1 suggests a good placebo effect due to a credible ritual, since it showed a lower MI than SMA and R, with SMA laying between group R and RMA. Its credibility is suggested also by the significant increase of Rizatriptan intake in RMA after the end of treatment (that is, from T_1 to T_2) when it reached the same values as SMA and R.

All groups underwent a sizable decrease of MI, which was below 36% of initial values at both T_1 and T_2. On average, it might reflect the effectiveness of Rizatriptan in comparison to relief therapy in baseline conditions, of which, unfortunately, we have not collected information: should Rizatriptan have improved relief therapy, the observed decrease of MI might be a mix of therapeutic and placebo effects. If so, it would have helped in making mock acupuncture credible too, since patients might not easily tell its effects from those of Rizatriptan.

TA only was able to provide long-lasting effects, strongly decreasing both MI and Rizatriptan intak e at both T_1 and T_2, while RMA provided a transient benefit at T_1 only, paralleled by changes in Rizatriptan intake. The transient effects observed in group RMA can therefore be assigned to a placebo effect, although the limit between a simple placebo and a true effect may not be so well defined. In fact, one cannot easily rule out that the closer physician-patient relationship yielded by the TCM approach might positively affect the treatment, through an iatroplacebogenesis rather than a simple placebo.[39]

In conclusion, our data suggest that traditional acupuncture is an effective tool for migraine prophylaxis: the syndrome differentiation according to TCM seems to work, although we do not yet know whether all TCM syndromes are so relevant as to call for a specific acupoint selection. Our protocol is the first attempt to check the effects of traditional acupuncture in migraine, providing a detailed report of acupoint selection according to TCM; however, our protocol can only be considered as a first, provisional attempt to merge TCM and Western medicine, in the definition of proper acupuncture treatment for migraine.

We do believe that acupoint selection plays a key role for effectiveness, and we are to face TCM in the process of acupuncture validation. It is the "true" acupuncture, with an enormous store of tradition and empirical knowledge, trickled out over 2,000 years of practice and still routinely used in Chinese hospitals. Western medicine and TCM are 2 deeply different worlds with different paradigms, which seem incompatible at a first glance. A correct approach to TCM has strong epistemological implications, but this cannot prevent us from trying to build a bridge between the 2, which is essential for acupuncture understanding.

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