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ORIGINAL ARTICLE

Single-blind, randomized, pilot study combining shiatsu and amitriptyline in refractory primary headaches

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Abstract Complementary alternative medicine, such as shiatsu, can represent a suitable treatment for primary headaches. However, evidence-based data about the effect of combining shiatsu and pharmacological treatments are still not available. Therefore, we tested the efficacy and safety of combining shiatsu and amitriptyline to treat refractory primary headaches in a single-blind, randomized, pilot study. Subjects with a diagnosis of primary headache and who experienced lack of response to ≥2 different prophylactic drugs were randomized in a 1:1:1 ratio to receive shiatsu plus amitriptyline, shiatsu alone, or amitriptyline alone for 3 months. Primary endpoint was the proportion of patients experiencing ≥50%-reduction in headache days. Secondary endpoints were days with headache per month, visual analogue scale, and number of pain killers taken per month. After randomization, 37 subjects were allocated to shiatsu plus amitriptyline ($n = 11$), shiatsu alone ($n = 13$), and amitriptyline alone ($n = 13$). Randomization ensured well-balanced demographic and clinical characteristics at baseline. Although all the three groups improved in terms of headache frequency, visual analogue scale score, and number of pain killers ($p < 0.05$), there was no between-group difference in primary endpoint ($p =$ ns). Shiatsu (alone or in combination) was superior to amitriptyline in reducing the number of pain killers taken per month ($p < 0.05$). Seven (19%) subjects reported adverse events, all attributable to amitriptyline, while no side effects were related with shiatsu treatment. Shiatsu is a safe and potentially useful alternative approach for refractory headache. However, there is no evidence of an additive or synergistic effect of combining shiatsu and amitriptyline. These findings are only preliminary and should be interpreted cautiously due to the small sample size of the population included in our study.
Trial registration 81/2010 (Ethical Committee, S. Andrea Hospital, Sapienza University, Rome, Italy).

Keywords Primary headache · Migraine · Shiatsu · Complementary alternative medicine · Amitriptyline

Background

Primary headaches are highly prevalent and disabling chronic conditions that cause disability, suffering, loss of work productivity and reduced quality of life [1–3]. The most common types of primary headaches are tension-type headache (TTH) and migraine, affecting 42 and 10% of adult population, respectively [1].

Pharmacological treatment of primary headaches may be acute or preventive, and patients with frequent or disabling attacks often require both approaches [4]. The purpose of preventive therapy is to reduce attack frequency, severity, and duration, and to act synergistically with abortive therapy to improve its effectiveness [5].

However, despite the development of many medications for treatment and prevention of migraine attacks, a number of patients find them ineffective and some other find them

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inappropriate because of their side effects [6, 7]. Moreover, all these drugs can be associated with adverse side effects that lead to early discontinuation of treatment [8, 9]. Drop-out rate are indeed reported to be high in most clinical trials (even in placebo arm), suggesting that these drugs are not well accepted by patients [10]. Furthermore, patients with frequent attacks may overuse medications, leading to migraine chronification and medication-overuse headache [11–13].

As a result, there is a growing interest in the development of non-pharmacologic approaches, such as complementary and alternative medicine [14]. In this regard, there is some evidence that acupuncture and acupressure, as well as behavioral interventions (e.g. relaxation, biofeedback, mindfulness) are beneficial [14–21], but their efficacy to date is limited by small trials, short follow-up periods, and a need for comparison or integration with established pharmacologic approaches [14, 21].

Shiatsu is a form of complementary and alternative medicine consisting of the pressure and scrubbing of the energy pathways in the body based on knowledge and application of energy to treat and relieve pain and pain-related symptoms [22]. Several health problems may be amenable to treatment by Shiatsu, including headaches, migraine and other painful conditions [23]. Shiatsu is considered an intrinsically safe treatment that has been reported to induce improvements in symptom severity and positive changes in health-related behaviour [23, 24]. However, the available evidence for shiatsu as an effective strategy to treat primary headaches is still poor, and most of the available data come from studies on acupuncture and acupressure [24].

Therefore, the aim of this study was to evaluate the efficacy and safety of shiatsu treatment in combination with a well-established pharmacological therapy (amitriptyline) in patients suffering from refractory primary headaches.

Methods

Study design and randomization

The present study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study protocol was registered and approved by the Ethical Committee Board of S. Andrea Hospital, Sapienza University, Rome, Italy (trial registration No. 81/2010). Each participant provided a written informed consent before any study-related procedure.

Patients regularly attending the Neurological Headache Centre of S. Andrea Hospital in Rome were considered for this 5-month single-blind, randomized, controlled pilot study. Patients who met all eligibility criteria (see below) were randomly allocated in a 1:1:1 ratio to receive combination of shiatsu and amitriptyline, shiatsu alone, or amitriptyline alone for three consecutive months (see Fig. 1). The randomization procedure was performed through computer-generated random numbers by an operator (LP) not involved in study measurements.

Eligibility criteria

To be considered eligible for this study, patients were required to fulfil all the following inclusion criteria: age from 18 to 55 years (inclusive); diagnosis of migraine with or without aura, tension-type headache (TTH) or chronic migraine without overuse according to the second version of the International Headache Criteria (ICHD-II) [25]; lack of response to at least two different prophylactic drugs (other than amitriptyline) regularly taken for three or more months [7]; be able to understand and comply with study requirements; voluntarily provide a written, dated and signed informed consent prior to any study procedure.

As exclusion criteria we also considered: pregnancy or breastfeeding; history of seizures; any clinically relevant gastrointestinal, respiratory, psychiatric, neurological, kidney, liver, cardiac diseases, bleeding disorder, other disease/condition or abnormal physical findings which could interfere with the study objectives or put the patient's safety at risk; psychiatric illness (including history of, or current, severe depressive disorders and/or suicidal ideation) that contraindicate the amitriptyline assumption or shiatsu.

Study assessments

Patients enrolled in the study underwent four visits as follows: (i) screening visit, about 1 month prior to randomization; (ii) baseline visit, in which patients were randomized in a 1:1:1 ratio to receive combination of shiatsu *plus* amitriptyline, shiatsu alone, or amitriptyline alone; (iii) end-of-treatment visit, about after 3 months from the screening visit, in which patients discontinued any treatment regardless of the group allocation; (iv) end-of-study visit, about 1 months after the end-of-treatment visit (5 months after the study entry). Therefore, three treatment periods were identified: a pre-treatment period, between the screening visit and the baseline visit; an on-treatment visit, between the baseline visit and the end-of-treatment visit; a post-treatment period, between the end-of-treatment visit and the end-of-study visit (see also Fig. 1).

At the screening visit, an experienced neurologist (GS) screened patients for eligibility, and made a diagnosis

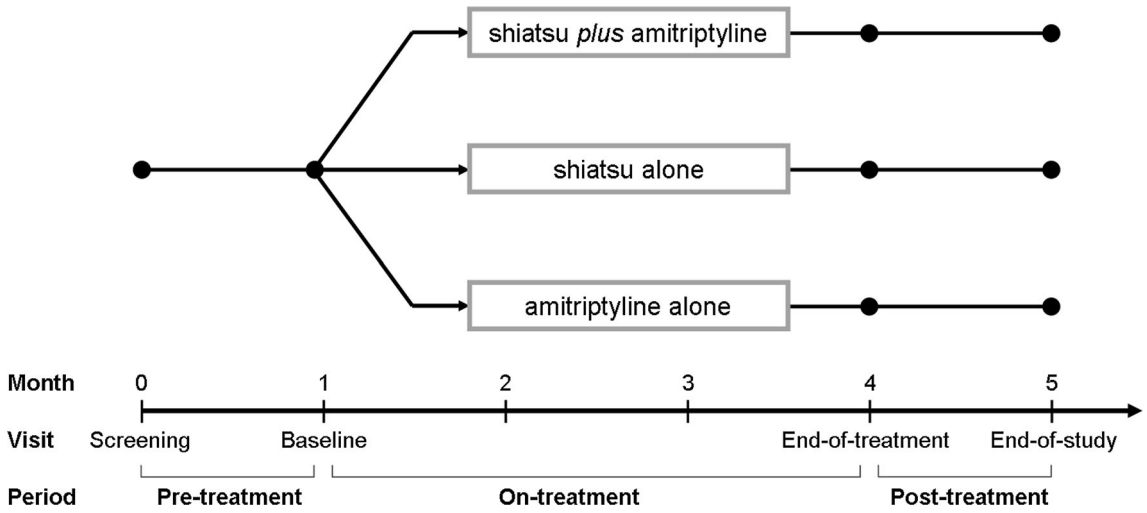

Fig. 1 Study protocol

according to the ICHD-II criteria [25]. Patients were also encouraged to contact the treating study team in case of any adverse events (AEs), defined as any untoward medical occurrence regardless of its causal relationship to the study intervention, or for any question regarding the study protocol. Adverse events were graded as mild (minimal or no treatment required and no interference with daily living activities); moderate (may require treatment and cause some interference with functioning); severe (systemic drug or other treatment required, interruption of daily living activities); life-threatening (immediate risk of death) (http://ichgcp.net/12-adverse-event-ae).

If a patient was considered eligible for the study, he/she was followed-up from other neurologists (VV and FO) who were blind to treatment allocation for the entire duration of the study; patients were instructed to not disclose to them their treatment. A daily diary was given to patients at each visit and had to be returned at next visit to prospectively collect the following data: (i) frequency of headache, measured as days with headache per month; (ii) headache severity, rated on a 0–10 point on a visual analogue scale (VAS), with higher scores indicating greater severity; (iii) numbers of pain killers (PKs) taken by patients (per month).

Interventions

Shiatsu treatment consisted of one 45-min session per week for a total of 12 sessions; it was administered at S. Andrea Hospital by the same expert operator (FP).

Shiatsu is a form of complementary and alternative medicine based on the theoretical framework of traditional Chinese medicine. The term "Shiatsu" derives from the Japanese language and it literally means "finger pressure". Shiatsu techniques include massages, gentle joint manipulations and mobilization, assisted stretching and pressure using fingers, thumbs, palms, elbows, knees and feet. According to the traditional Chinese medicine, shiatsu exerts its effect by correcting imbalances in energy, i.e. bringing energy to areas of the body that need energy and releasing energy from areas that are blocked [22]. However, few studies also suggest that shiatsu is able to enhance endorphin release and to decrease the levels of stress-related hormones, thereby stimulating relaxation [26–28].

Oral amitriptyline was started at a dosage of 5 mg daily and was increased up to 10 mg daily after 1 week. In case of side effects, patients were instructed to reduce the dosage to 5 mg daily. If the side effects continued to be not solved, they had to return to the hospital for an unscheduled visit. Amitriptyline was discontinued after a de-titration period of 1 week.

Study endpoints

The primary endpoint was the proportion of patients experiencing a more than 50% reduction in days with headache per month [7], as estimated by comparing the headache frequency during the on-treatment period (average number of days with headache per month over 3 months), and during the post-treatment period, with the headache frequency during the pre-treatment period.

Additional endpoints were the median changes in days with headache per month, VAS score, and number of PKs taken per month, as measured throughout the entire study period.

The proportion of patients who reported any adverse event was also reported.

Statistical analysis

Given the exploratory nature of this pilot trial, no sample size analysis was performed.

Data are presented as proportion for categorical variables, and as mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables, as appropriate.

The analysis was restricted to the participants who fulfil the protocol in the terms of the eligibility, and completed all the scheduled visits, according to the per protocol principle. Therefore, patients who dropped-out or lost to follow-up were not analyzed.

Well-balancing of the three treatment groups after randomization were tested using the Chi-squared and the Kruskall–Wallis *H* tests (with the Dunn test for post hoc comparisons), for continuous and categorical variables, respectively.

The primary endpoint was investigated using a logistic regression analysis, adjusted for gender, age and pre-study days with headache per month (measured in the pre-treatment period prior to randomization).

To investigate the additional endpoints, between-arm differences in days with headache per month, VAS score and number of PKs were tested by the Kruskall–Wallis *H* test (with the Dunn post hoc test) by comparing the median percentage changes from pre-treatment period to on-treatment period and post-treatment period.

The occurrence of adverse events as afore defined was also descriptively reported.

Two-tailed p values less than 0.05 were considered as significant. All analyses were carried out using the Statistical Package for Social Sciences, version 16.0 (IBM SPSS, Chicago, IL, USA).

Results

Participants

From September 2010 to April 2011 a total of 50 patients were assessed for eligibility; out of these, five did not met the eligibility criteria and four declined to participate. Therefore, 41 were randomized to receive shiatsu *plus* amitriptyline ($n = 13$), shiatsu alone ($n = 14$), and amitriptyline alone ($n = 14$). Four patients did not return to follow-up visit and then were considered lost to follow-up (two in shiatsu *plus* amitriptyline group, one in shiatsu group, and one in amitriptyline group; see also the study flow-chart; Fig. 2).

Therefore, a total of 37 patients (31 women, 6 man) with a mean age of 39.8 (11.5) years (ranging from 18 to 55 years) and diagnosed as affected by migraine without ($n = 15$) and with aura ($n = 5$), frequent episodic TTH ($n = 5$) or chronic migraine ($n = 12$) were analyzed. The treatment allocation for the analyzed patients was as follows: shiatsu *plus* amitriptyline ($n = 11$), shiatsu alone ($n = 13$), and amitriptyline alone ($n = 13$). The three treatment arms were comparable in terms of baseline demographic and clinical characteristics (p values ≥ 0.2 for all comparisons) (see Table 1). Adherence to study interventions (including amitriptyline assumption) was very high and none of the patients who underwent shiatsu (alone or in combination) missed even a session.

Efficacy

At the end of end-of-treatment visit, the proportions of patients experiencing a more than 50% reduction of days with headache per month compared with the pre-treatment period (primary endpoint) were 55, 69, and 62% in shiatsu *plus* amitriptyline arm, shiatsu alone arm, and amitriptyline alone arm, respectively, without any statistically significant between-arm difference. At end-of-study visit (i.e. about 1 month after stopping the treatment), the proportions of patients who continued to have a more than 50% reduction of days with headache per month compared with the pre-treatment period were 45, 54 and 46% in shiatsu *plus* amitriptyline arm, shiatsu alone arm, and amitriptyline alone arm, respectively. Even in this latter case, we found no statistically significant between-arm difference (see also Table 2).

Additional endpoints were summarized in Table 3.

All treatment groups experienced a significant improvement in terms of days with headache per month, VAS score, and number of PKs during both on-treatment period and to post-treatment period (all p values less than 0.05).

There were no statistically significant between-arm difference in median changes from pre-treatment period to on-treatment period and to post-treatment period in terms of frequency attack and VAS score. By contrast, those patients who received shiatsu alone experienced a greater reduction in the number of PKs per month during the on-treatment period when compared to the pre-treatment period ($p = 0.024$). Post-hoc analyses revealed that amitriptyline alone was less effective than either shiatsu plus amitriptyline (median change -58 versus -69%, respectively; $p = 0.029$) and shiatsu alone (median change: -58 versus -80%, respectively; $p = 0.012$). Lastly, no significant between-arm difference was found in the number of PKs per month during the post-treatment period, indicating no retention of the effect of shiatsu (alone or in combination with amitriptyline) on this outcome.

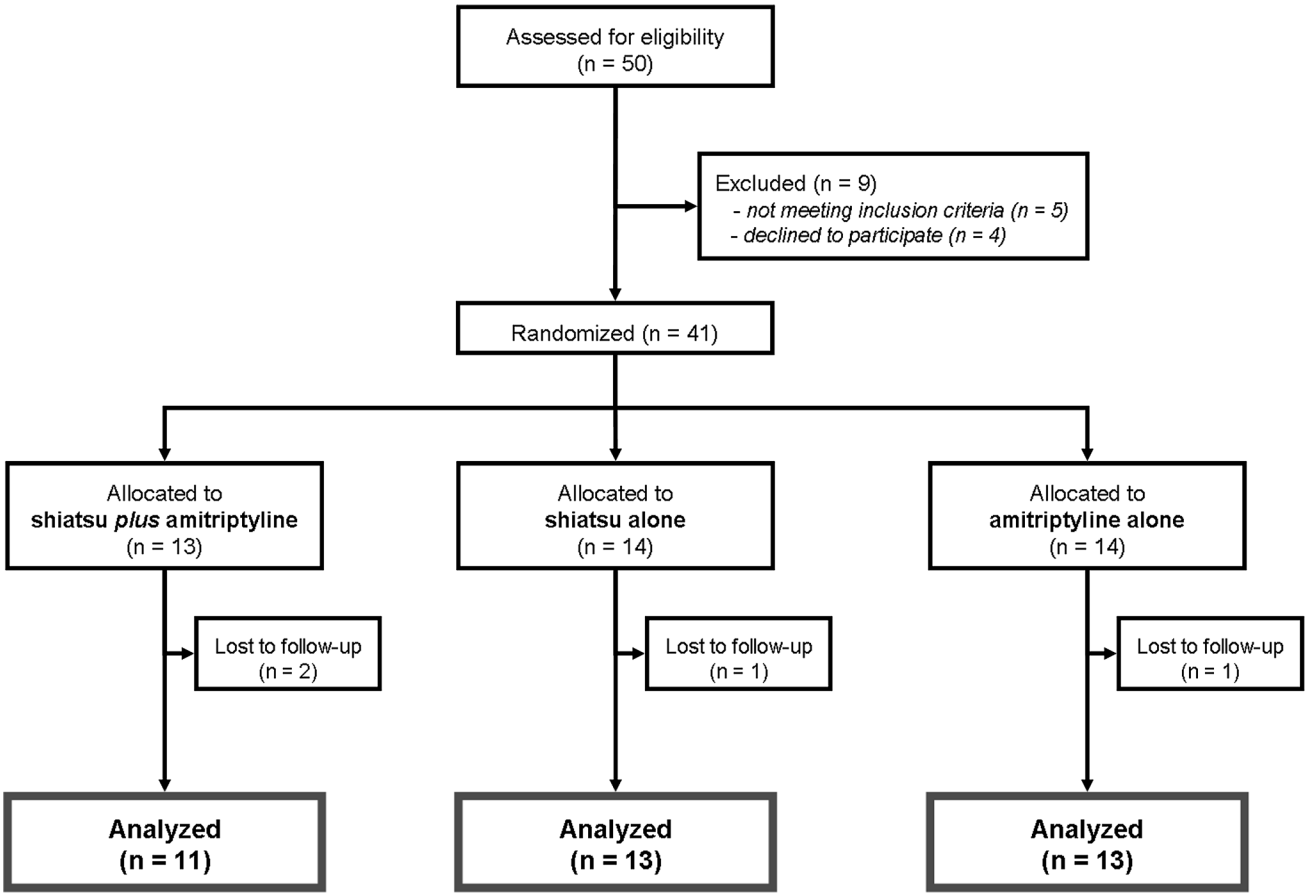

Fig. 2 Study flow-chart

Table 1 Patients' characteristics at baseline visit

	Shiatsu plus amitriptyline ($n = 11$)	Shiatsu ($n = 13$)	Amitriptyline ($n = 13$)
Gender, *n*, female:male	12:1	10:1	9:4
Age, years	36.5 (11.7)	37.1 (11.5)	46.2 (11.1)
ICHD-II diagnosis, *n*			
Migraine without aura (1.1)	4	5	6
Migraine with aura (1.2)	1	2	2
Frequent episodic tension-type headache (2.2)	1	2	2
Chronic migraine (1.5.1)	5	4	3
Days with headache per month	13.8 (7.3)	13.5 (6.7)	16.8 (7.0)
VAS score	8.8 (1.3)	8.9 (1.2)	8.8 (1.0)
No. of pain killers per month	13.3 (8.0)	12.2 (4.2)	14.8 (6.7)

All data are expressed as mean (standard deviation), unless indicated otherwise

All p values are ≥ 0.2

ICHD-II second version of the international headache criteria, *VAS* visual analogue scale

Safety

Over the course of the study, seven (19%) patients reported at least one AE.

As shown in the Table 4, all AEs ($n = 9$) occurred in groups treated with amitriptyline (alone or in combination with shiatsu) during the on-treatment study period and were consistent with the well-known side effect profile of

Table 2 Proportion of patients experiencing a more than 50% reduction of days with headache per month compared with the pre-treatment period (primary endpoint)

	Shiatsu plus amitriptyline ($n = 11$)	Shiatsu ($n = 13$)	Amitriptyline ($n = 13$)
On-treatment period			
n (%)	6 (55%)	9 (69%)	8 (62%)
OR (95% CIs)	0.4 (0.1–3.2)	1.2 (0.2–6.9)	1.0
p	0.5	0.8	Ref
Post-treatment period			
n (%)	5 (45%)	7 (54%)	6 (46%)
OR (95% CIs)	2.0 (0.3–14.6)	2.3 (0.4–13.6)	1.0
p	0.5	0.4	Ref

95% CIs 95% confidence intervals, *OR* odds ratio

Table 3 Additional endpoints: mean values and their relative percentage changes throughout the study

	Shiatsu plus amitriptyline ($n = 11$)	Shiatsu ($n = 13$)	Amitriptyline ($n = 13$)
Days with headache per month			
Pre-treatment period	13.8 (7.3)	13.5 (6.7)	16.8 (7.0)
On-treatment period	8.1 (6.2)	4.6 (3.5)	7.6 (5.8)
% change from pre-treatment period, median (IQR)	−47 (−72, −37)	−67 (−77, −30)	−50 (−77, −36)
Post-treatment period	9.2 (8.0)	6.2 (5.2)	9.8 (6.1)
% change from pre-treatment period, median (IQR)	−38 (−70, −10)	−50 (−25, −88)	−40 (−69, −6)
VAS score			
Pre-treatment period	8.8 (1.3)	8.9 (1.2)	8.8 (1.0)
On-treatment period	6.0 (1.8)	5.3 (2.3)	6.2 (1.3)
% change from pre-treatment period, median (IQR)	−30 (−56, −14)	−38 (−20, −50)	−31 (−38, −16)
Post-treatment period	6.6 (2.2)	6.4 (3.6)	6.9 (1.5)
% change from pre-treatment period, median (IQR)	−30 (−40, 0)	−15 (−50, 0)	−20 (−24, −12)
No. of pain killers per month			
Pre-treatment period	13.3 (8.0)	12.2 (4.2)	14.8 (6.7)
On-treatment period	6.4 (5.8)	2.4 (1.7)	6.8 (5.8)
% change from pre-treatment period, median (IQR)	−69 (−75, −50)	−80 (−100, −65)	−58 (−80, −35)*
Post-treatment period	7.9 (5.9)	5.8 (5.2)	8.5 (4.7)
% change from pre-treatment period, median (IQR)	−35 (−70, 0)	−60 (−30, −80)	−35 (−63, −18)

All values are mean (SD), unless indicated otherwise

IQR interquartile range, *VAS* visual analogue scale

* $p = 0.024$ by the Kruskall–Wallis *H* test; Dunn post hoc test: $p = 0.029$ for shiatsu plus amitriptyline versus amitriptyline alone, $p = 0.013$ for shiatsu alone versus amitriptyline alone

this drug. All these AEs were graded as mild, thus no patient required treatment discontinuation, but only a reduction of amitriptyline dosage.

Notably, no AEs occurred in the shiatsu alone arm, indicating that it was a well-tolerated technique.

Discussion

In this pilot study we investigated whether the combination of a complementary alternative medicine (such as shiatsu) with a standard-of-care drug (such as amitriptyline) was more effective than either intervention alone in patients affected by primary headache and refractory to other standard pharmacological treatment [7]. Although our findings demonstrate that shiatsu is a very well-tolerated approach and that combination with pharmacological drugs is feasible, the present study reveals neither an additive or synergistic effect, nor a superior efficacy of the combination strategy over either intervention alone. The primary endpoint of this study was not met, since the proportion of patients who had more than 50% reduction in days with headache per month was lower in shiatsu *plus* amitriptyline (55%) than in shiatsu alone (69%) and amitriptyline alone (62%) arms. Therefore, likely due to the small sample size, we cannot definitively elucidate if our study was

Table 4 Summary of the study-related adverse events

	Shiatsu plus amitriptyline ($n = 11$)	Shiatsu ($n = 13$)	Amitriptyline ($n = 13$)
Patients with adverse events	3	0	4
No. of adverse events	5	0	4
Study discontinuation due to adverse events	0	0	0
Serious adverse events	0	0	0
Description of adverse events			
Drowsiness	1	0	3
Tachycardia	2	0	1
Dry mouth	1	0	0
Weight increase	1	0	0

underpowered to catch the superiority of the combination strategy on the primary endpoint, or if combining shiatsu and amitriptyline really did not provide any advantage.

In spite of this, patients randomized to shiatsu (alone or in combination) experienced a significant benefit on headache frequency and severity (as assessed by VAS score), and PKs assumption, supporting the notion of an anti-nociceptive effect of shiatsu possibly driven by an enhanced endorphin release that is, in turn, mediated by stimulation of afferent type I and II nerve fibers [27, 28]. Endorphins block chemoreceptor trigger zone (CTZ) signals that is known to be involved in the physiopathology of migraine [29]. It has been also postulated that Shiatsu promotes enkephalin-mediated release of monoamine neurotransmitters (serotonin and norepinephrine) through nerve impulses sent to the periaqueductal gray area and stimulates the pituitary gland to release endorphins and adrenocorticotropic hormone into the bloodstream and cerebrospinal fluid [30]. However, the effect of shiatsu on melatonin and beta-endorphin levels is still controversial [31].

The effect of acupressure in reducing headache-related nausea and vomiting, as well as prescription of analgesics and symptomatic drugs, has been documented in the literature [18–20, 32, 33]. Consistently, we found a slight, but significant effect of shiatsu (alone or in combination with amitriptyline) on the number of PKs taken during the on-treatment period when compared with amitriptyline alone. On the basis of these findings, and with the available sample size, a power of 30% at the two-sided 5% a level was achieved in detecting a more significant effect of shiatsu than amitriptyline on the number of PKs. Hypothetically, a future clinical trial should enrol 126 patients (63 per group) to reach a 80% statistical power in demonstrating that shiatsu is superior to amitriptyline.

The reasons for which the reduction in the number of PKs taken by patients did not transfer into a significant lower number of days with headache per month and lower VAS score deserve further speculations. Notably, the superior effect of shiatsu (whit respect to amitriptyline) in reducing the number of PKs taken per month was not sustained once the intervention was discontinued (i.e. during the post-treatment period). This latter finding raises the question that shiatsu might be considered even more useful as abortive rather than preventive treatment.

As expected, a relevant proportion of patients who received amitriptyline (7/24, 29%) presented mild side effects who rapidly disappeared after halving the daily dosage. By contrast, shiatsu was well tolerated by patients, without any AE or discomfort, according to literature data [23, 24].

Limitations of the present study, other than the afore mentioned low sample size, mainly encompass the lack of data on patients' anxiety and depression (which are recognized to have a strong impact on headache severity and chronification [34]) and the absence of blinding for patients who were fully aware of the received treatment. A future study design would compare "sham" pressure points with "true" pressure points to overcome this bias. Furthermore, the occurrence of AEs clearly attributable to amitriptyline treatment (see also Table 4) might have further biased the blindness of the evaluating neurologists. Lastly, our results might have been also affected by the fact that the present study was conducted in 2010–2011, when the most recent diagnostic criteria (ICHD-III) [35] and the new definition of refractoriness [36] were not available yet.

In conclusion, despite these limitations, to our knowledge there are no other studies investigating the efficacy and feasibility of combining shiatsu *plus* amitriptyline. Although we found no additive or synergistic effect, shiatsu alone or in combination was not inferior to amitriptyline in reducing the frequency and severity of refractory primary headaches, and even superior to amitriptyline in reducing the need of taking abortive treatments. Future efforts are now warranted to better define the role of shiatsu and other similar complementary alternative medicine in the management of primary headaches refractory to standard prophylactic drugs.

Conclusion

This article presents the findings from a single-blind, randomized trial investigating the effect of combining shiatsu plus amitriptyline for patients with refractory headaches. Although the combination did not provide any additive/synergistic effect, the shiatsu was superior to amitriptyline in reducing the number of pain killers taken per month. There was no safety concern for shiatsu (alone or in combination).

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Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

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