Clinical effectiveness of osteopathic treatment in chronic migraine: 3-Armed randomized controlled trial

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KEYWORDS
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Summary
Objective: To assess the effectiveness of OMT on chronic migraineurs using HIT-6 questionnaire, drug consumption, days of migraine, pain intensity and functional disability.
Design: 3-Armed randomized controlled trial setting: all patients admitted in the Department of Neurology of Ancona's United Hospitals, Italy, with a diagnosis of migraine and without chronic illness, were considered eligible for the study.
Interventions: Patients were randomly divided into three groups: (1) OMT + medication therapy, (2) sham + medication therapy and (3) medication therapy only. Patients received 8 treatments in a study period of 6 months.
Main outcome measures: Changing from baseline HIT-6 score.
Results: 105 subjects were included. At the end of the study, ANOVA showed that OMT significantly reduced HIT-6 score (mean change scores OMT—conventional care: -8.74; 95% confidence interval (CI) -12.96 to -4.52; $p < 0.001$ and OMT—sham: -6.62; 95% CI -10.85 to -2.41; $p < 0.001$), drug consumption (OMT—sham: RR = 0.22, 95% CI 0.11—0.40; OMT—control: RR = 0.20, 95% CI 0.10—0.36), days of migraine (OMT-conventional care: $M = -21.06$; 95% CI -23.19 to -18.92; $p < 0.001$ and OMT—sham: -17.43; 95% CI -19.57 to -15.29; $p < 0.001$), pain intensity (OMT—sham: RR = 0.42, 95% CI 0.24—0.69; OMT—control: RR = 0.31, 95% CI 0.19—0.49) and functional disability ($p < 0.001$).

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Conclusions: These findings suggest that OMT may be considered a valid procedure for the management of migraineurs.

The present trial was registered on www.ClinicalTrials.gov (identifier: NCT01851148).

Introduction

Migraine is a serious public health concern of considerable consequences to both the migraineur and society. The overall migraine prevalence in Europe is approximately 10—15%.[1,2] Although migraine is considered a benign disorder, the annual cost of migraine-related lost productivity is extensive.[3—5]

The International Classification of Headache Disease (ICHD-II, 2004) ranks headache in primary and secondary forms. Furthermore the ICHD-II divided migraine into episodic and chronic according to the number of days per month (cut-off of 15 days).

Migraine attacks are usually characterized by a unilateral and pulsating severe headache, lasting 4—72 h, and are often associated with nausea, phono- and photophobia. In at least 1 out of 5 subjects, the attacks are anticipated by transient neurological symptoms, described as aura.

Migraine etiology has been proved to be genetic (up to 50% of cases),[6] but multifactorial epigenetic mechanisms may be outlined.

From a neurophysiological prospective, there is accumulating evidence to support that the central sensitization plays a critical role in migraine pathogenesis.[7,8] This has been proved by studies showing a functional alteration of key centers in the central nervous system (CNS), in particular the trigeminovascular nuclei.[6,9—14]

As far as the neurogenic inflammation of meninges is considered, high level of cytokines is released during migraine attacks[13,14] that in turn activates specific neural pathways transmitting pain signals to the trigeminovascular system and vegetative nervous system (VNS) nuclei.[15,16] This condition may predispose to VNS dysfunctions which have been suggested to be one of the causes of headache.[11]

Therefore, dysfunctional nervous structures, inflammatory condition and functional alteration of the VNS may be responsible for the pain and contribute to migraine pathophysiology.

Recent studies provided information about the possible association between manual therapies in particular osteopathic manipulative treatment (OMT) and its effects on migraine. Voigt et al. carried out an RCT showing the effects of OMT on migraineurs' quality of life. The author claimed a significant improvement in the quality of life parameters as well as a reduction of pain.[17]

Another piece of research evaluated the effects of OMT in patients with headaches. Patients who received 8—12 osteopathic sessions showed a significant reduction of pain and frequency of attacks.[18]

In 2006 Anderson and Seniscal compared the effects of OMT to progressive muscular relaxation exercises on patients with tension-type headache. Subjects who underwent both treatments, showed significant improvement on joint and myofascial stiffness and reduction of pain compared to exercise only.[19]

Despite the number of studies conducted, evidence to support the effectiveness of OMT on chronic migraine remains elusive. Thus the present study aimed to test the effectiveness of OMT on a sample of adult chronic migraineurs by measuring the baseline changes of the headache impact test (HIT-6) questionnaire.

Materials and methods

The aim of this 3-armed randomized control study was to determine the extent to which OMT was effective in improving the HIT-6 score on a sample of subjects affected by chronic migraine. In addition, the variation of monthly days with migraine, pain intensity, drug assumption and functional disability was measured. The trial was registered on www.ClinicalTrials.gov (identifier: NCT01851148) and approved by the institutional review board of Ancona's hospital.

Population

This study was carried out in the Department of Neurology of Ancona's United Hospitals in the period between March 2010 and November 2011. Patients admitted in the unit with the following criteria were included: diagnosis of chronic migraine according to ICHD-II criteria, lasting 15 or more days per month for more than 3 months in the absence of medication overuse and not attributable to any other disease; pain refractory to preventive medications; headache pattern has been present for 12 months or longer; current acute and prophylactic headache medication regimens have been stabilized for four weeks prior to preliminary enrolment visit; headache of any pain intensity (0—10 scale) on days over 15 during each four-week period; aged between 18 and 60 years old of either sex. Exclusion criteria applied were: patients with secondary forms of headache, chronic illness, psychiatric disorders, postmenopausal women, aged under 18 and over 60 years old, with significant psychological signs on examination and/or history, or serious drug habituation or behavioral issues that in physician's judgment makes the subject inappropriate for study, alternative treatment to treatment migraine pain (e.g. acupuncture, massage, biofeedback) and previous experience of osteopathic treatment.

Interventions

The sample was randomly divided into three groups: OMT + medication therapy (OMT group), sham + medication therapy (sham group) and medication therapy only (control group).

The OMT group received, in addition to the conventional care, 8 osteopathic sessions during the 6-month treatment period (24 weeks).

Techniques used were myofascial release, balanced ligamentous tension, balanced membranous tension and cranial-sacrum (Table 1).[20,21] A need-based patient treatment approach, that is treatment plan based on findings derived from the osteopathic evaluation and not based on a pre-determined protocol, was applied to the study group. Criteria considered for osteopathic evaluation and treatment were tissue alteration, asymmetry, range of motion and tenderness parameters.

$N = 6$ osteopaths, certified by the Italian Register of Osteopaths, graduated from the same Italian school (Accademia Italiana Osteopatia Tradizionale) and with similar educational curricula, were in charge to administer osteopathic treatments and collect osteopathic records. Each osteopath was responsible for the same patient from enrolment to the end of the study period.

The sham group received a false OMT, in addition to drug care. For this trial, sham therapy mimicked the osteopathic care in terms of evaluation and treatment. Sham evaluation overlapped the osteopathic structural evaluation procedure. A screening of the patient was performed utilizing the conventional osteopathic manual tests without putting any intention in the diagnosis. Sham treatment used light manual contact to ''treat'' the subject and was administered with subject lying supine on the treatment table. The anatomical areas contacted were different across sessions and were based on the personal choice of the operator. There was no standardized protocol in terms of number, duration and typology of touching regarding the manual bodily contacts. This was based on a precise rationale, which included the variability of the touch, the length of the study period, the number and duration of sessions, as important cofactors to successfully blind patients to the sham. In addition, the practitioner diverted his/her attention by progressively subtracting in silence seven to a given number.[22] $N = 6$ osteopaths, ROI certified, performed the sham therapy. Sham + medication therapy group received 8 extra real OMT sessions after the end of the study.

Osteopathic and sham therapy sessions lasted 30 min and were scheduled as following: weekly for the first two sessions, biweekly for the subsequent two, then monthly for the remained four sessions.

Unlike subjects in the OMT and sham groups, who were required to maintain stable medication regimens (although frequency and dose of acute medications could change if necessary), subjects in the control group were able to adjust, change and optimize medication regimens as directed by the physician.

Randomization, blinding and masking

All patients entering the study were randomly allocated to the OMT, sham and conventional care arms using R software as computer random number generator.[23]

The type of randomization was permuted-block (ratio 1:1:1). The process of randomization was performed by an external operator from the coordinating center.

Clinical evaluations were performed at entry (T0) and after 24 weeks (T1) by the same neurologist who was blinded to the patient's allocation and outcomes. Moreover, unit department staff was unaware about patient's allocation. The only practitioners who were aware about treatments were the osteopaths who performed OMT or sham therapy.

Clinical and osteopathic data were collected using an ad-hoc software to avoid possible data contaminations. Data export was performed by the statistician from the coordinating center. The blind-to-treatment allocation was tested using a post-treatment single question telephone survey conducted by the neurologist.

Outcome measures

Primary outcome of the study was changes from the baseline of the HIT-6 score. The latter is a validated questionnaire that measures the impact of headaches on person's daytime activities.[24] The HIT-6 was administered at T0 and T1. To test the difference between the three groups, two scores were used: the overall HIT-6 score and the difference between T1 and T0 in the HIT-6 score. The latter was used to compare results with the minimal important difference (MID) index. Coeytaux et al.[25] established a MID of −2.3 points between baseline and post-treatment HIT-6 score to affirm clinical relevant effects of a given procedure.

Secondary outcome measures were taken from the migraine diary. At entry, patients received a standardized migraine diary focusing mainly on: days per month with migraine, severity of pain (4-point Likert scale: 0 indicates no pain; 1, mild; 2, moderate; 3, severe), amount of rescue medication and functional disability (0 indicates able to work or function normally; 1, working ability mildly impaired; 2, working ability moderately impaired; and 3, working ability severely impaired). Adverse effects of OMT were an item in the headache diary. The length of baseline measurements was 4 weeks.

Statistical analyses

The primary analysis was based on intention-to-treat methods. Missing data was handled using last observation carried forward techniques. Sample size calculation used a difference in HIT-6 score of 5 points between groups and 27 within groups with a power of 90% and an alfa equal to 0.05. The result $N = 35$ was considered the sample size for each group.

The assessment of homogeneity of variance was performed using Brown−Forsythe- and Levene-type tests.

Results were expressed in terms of point estimate and 95% of confidence interval (CI). Arithmetic mean, standard deviation, percentage, range, median and interquartile range were used. Binary data was compared using the χ^2 test.

Two-factorial analysis of variance (ANOVA) with the main factors group and time was conducted to test the difference in variance among the three groups having defined an alfa level less than 0.05. Tukey post hoc analysis was applied for any statistical difference resulted from ANOVA. Analysis of covariance (ANCOVA) was preformed to test the independent effect of OMT on the primary outcome considering other covariates.

Table 1 Description of osteopathic techniques used.

Type of technique	Explanation
Myofascial release	A system of soft manual treatment directed to the muscles and fascia which engages the detection of restriction of motion and continual palpatory feedback to achieve release of myofascial tissues
BLT	A complex of light manual movements that allows the practitioner to test the tension of ligaments, disengage the area with SD, find the point of balance and treat the area according to the existing range of motion
BMT	Same as BLT but applied to the cranial field
Cranial-sacrum	An approach that uses soft touch to explore the primary respiratory mechanism and treat any imbalance between sacrum (pelvis) and cranial bones motility

BLT, balanced ligamentous tension; BMT, balanced membranous tension; SD, somatic dysfunction.

Table 2 General characteristics of the study population at the baseline.

	OMT	Sham	Control
Age[a]	36.9 (9.3)	40.7 (8.7)	38.4 (9.9)
BMI[a]	22.6 (3.0)	23.8 (4.2)	24.4 (3.8)
Male[b]	8 (22.9)	13 (37.1)	15 (42.9)

[a] Mean (±sd).
[b] n (%).

Repeated measures ANOVA was used to explore the differences between intermediate time points. R statistical package used for pairwise test was multcomp.[26]

Ordinal data (pain, functional disability) were analyzed using Kruskall−Wallis test and two-way repeated measures ANOVA on ranks (Friedman test). In either instance, post hoc Bonferroni−Dunn correction was used to manage multiple comparisons. The percentage of subjects who were free of pain, defined as pain intensity reduced to zero, and free of medications were computed. Relative risk was calculated.

The statistical software used was R (v. 2.15.2).[23]

Results

225 subjects were considered eligible for the study. After the application of exclusion criteria $N = 105$ patients entered the study and were randomly divided into three groups ($n = 35$ in each arm): OMT, sham and control groups (Fig. 1). No subjects were excluded from the analysis; no dropout and missing data were recorded. At baseline, no statistically significant imbalances were found between the three groups except for severity of pain (Tables 2 and 3).

At the end of the study period, ANOVA showed a statistically significant difference on the overall HIT-6 score between the three groups $F_{(2,102)} = 12.58$, $p < 0.001$.

Tukey post hoc comparisons indicated that OMT group was statistically different from control (−8.74; −12.96, −4.52; $p < 0.001$) and sham group (−6.62; −10.85, −2.41; $p < 0.001$) (Table 3).

Considering pre-post delta variation in HIT-6 score, ANOVA revealed a statistical significance difference between the three samples $F_{(2,102)} = 16.08$, $p < 0.001$.

Tukey post hoc analysis showed that OMT group had a statistically significant reduction compared to control (−8.40; −11.94, −4.86; $p < 0.001$) and sham (−4.83; −8.36, −1.29; $p < 0.001$). Sham group did not demonstrate any

significant difference compared to control (−3.12; −6.61, 0.32; $p = 0.08$).

At the end of the study period, ANCOVA showed that OMT is independently associated to a change in the overall HIT-6 score [$M = -9.07$; 95% CI −12.54, −5.60; $p < 0.001$] as well as age and gender (Table 3). Considering pre-post delta variation in HIT-6, OMT produced a significant difference compared to other confounders [−8.89; −11.87, −5.89; $p < 0.001$]. In addition, sham group resulted independently associated to a pre-post delta variation of HIT-6 [−3.57; −6.49, −0.64; $p = 0.02$].

Considering migraine days per month, the three groups differed significantly at the end of the study period $F_{(2,102)} = 314.1$, $p < 0.001$ (Table 3 and Fig. 2). Tukey post hoc analysis demonstrated that OMT group significantly reduced the frequency of migraine (OMT vs control: $M = -21.06$; 95% CI −23.19, −18.92; $p < 0.001$ and OMT vs sham: −17.43; −19.57, −15.29; $p < 0.001$). Sham group was significantly different from control group: −3.63; −5.77, −1.49; $p < 0.001$.

Taking into account drug use, OMT significantly reduced the number of subjects taking medications (OMT $n = 7$, sham $n = 32$ and control $n = 35$, $p < 0.001$) (Table 3), decreasing, therefore, the relative risk (OMT−sham: RR = 0.22, 0.11−0.40; OMT−control: RR = 0.20, 0.10−0.36).

Pain intensity differed significantly among groups (Table 3). Pairwise comparisons showed significant imbalances between all samples ($p < 0.001$). The number of people free from pain differed significantly among groups ($p < 0.001$), as well as the RR of perceiving pain (OMT−sham: RR = 0.42, 0.24−0.69; OMT−control: RR = 0.31, 0.19−0.49).

Disability score varied significantly between groups at the end of the study (Table 3). Bonferroni−Dunn test demonstrated differences between all pairwise comparisons ($p < 0.001$).

Repeated measure analyses

Repeated measures within group ANOVA showed statistically difference among time points in the OMT group in terms of migraine days ($F_{(6,34)} = 25.38$, $p < 0.0001$), intensity of pain and disability score ($p < 0.001$). Patients in the sham arm showed an unchanged overall trend ($F_{(6,34)} = 1.02$, $p = 0.41$) although a reduction until the third month was recorded. The control group did not show any difference during 6 months ($F_{(6,34)} = 0.14$, $p = 0.99$) (Fig. 2).
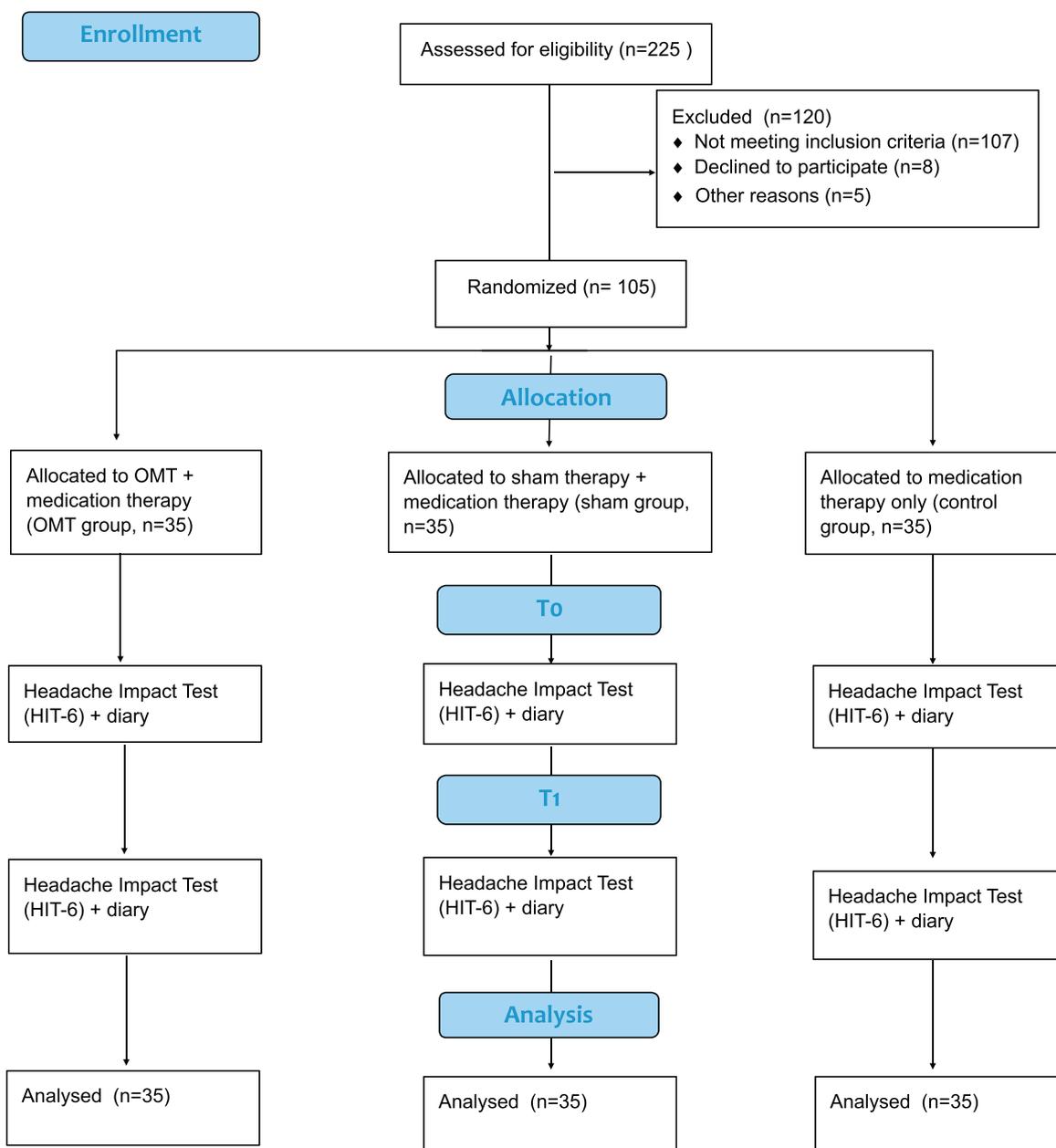
Figure 1   Flow chart of the study.

No study participant reported any adverse effects of the treatment. Among 35 patients allocated in the sham group, none of them was able to correctly guess the nature of the treatment.

Discussion

The principal finding of this three armed RCT was that OMT is effective in reducing the HIT-6 score by 8 and 6 units compared to control and sham therapy respectively.

Migraine attacks, use of drugs, pain and disability scores were significantly reduced in the OMT group.

Taking the MID value[25] as a benchmark to interpret our results, OMT showed a significant improvement in the migraineurs' quality of life. Moreover sham group significantly reduced the HIT-6 score compared to the conventional care. The magnitude of the results suggests that the sham procedure may be clinically effective (pre-post delta HIT-6 = −3.57). As confirmed by the recent literature, the expected disadvantages for the intervention provided in the trial were null and no major side effects were observed.[27]

To the best of our knowledge, this OMT trial is the largest ever conducted on migraine adult patients. Strengths in the methodology of this study include: allocation concealment, blinding of outcome assessor, outcomes reporting, high levels of treatment adherence and clinical interpretation of results. Sham treatments were adequately blinded and patients did not report any complain during the study

Table 3 Analysis of outcomes by study groups.

Variables	Baseline			End of the study (6 months)			Between-group differences at 6 months			Post hoc analysis
	OMT	Sham	Control	OMT	Sham	Control	OMT–control	OMT–sham	Sham–control	
HIT-6[a]	58.5 (5.8)	59.9 (8.0)	58.9 (7.0)	52.9 (7.7)	59.1 (7.5)	61.6 (7.4)	−8.74 (−12.9 to −4.52)[d]	−6.62 (−10.85 to −2.41)[d]	−2.32 (−6.01 to 1.40)[d]	a,b
Patients taking medications[b]	35 (100)	35 (100)	35 (100)	7 (20)	32 (91.4)	35 (100)	0.20 (0.10–0.36)[e]	0.22 (0.11–0.40)[e]	0.92 (0.82–1.03)[e]	a,b
Days of migraine/month (n)[a]	22.5 (5.2)	22.3 (5.0)	22.5 (5.2)	1.2 (1.9)	18.6 (4.6)	22.3 (4.2)	−21.06 (−23.19 to −18.92)[d]	−17.43 (−19.57 to −15.29)[d]	−3.63 (−5.77 to −1.49)[d]	a,b,c
Severity of pain[c]	3 (2–4)	3 (1–4)	3 (1–4)	0 (0–1)	2 (0–3)	3 (1–4)	3 (0–3)	2 (0–2)	1 (0–2)	a,b
Functional disability[c]	3 (2–3)	3 (2–3)	3 (2–4)	0 (0–1)	2 (1–3)	3 (2–3)	3 (0–3)	2 (0–3)	1 (1–3)	a,b

a Mean (±sd).
b n (%).
c Median (IQR).
d ANCOVA test – mean (95% CI) adjusted per baseline values, age, gender, BMI.
e Relative risk (95% CI) adjusted per baseline values, age, gender, BMI.
Post hoc tests: $p < 0.05$ for OMT vs sham (a), OMT vs control (b) and sham vs control (c).
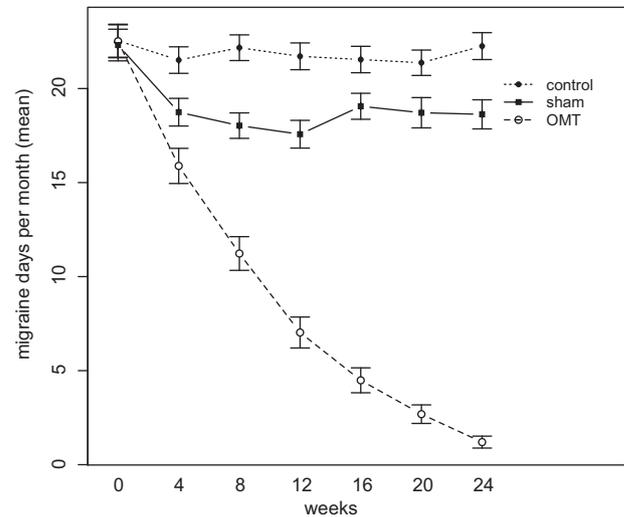

Figure 2 Number of migraine days per month during the all study period. omt, osteopathic manipulative treatment. Values reported are mean ± sd.

period. This was possibly due to the fact that patients were naive to osteopathy.

However, some apparent limitations have to be addressed such as osteopathic practitioners were not blinded from allocation and sham treatment was performed by osteopaths. In addition, diary data, co-morbidities and concomitant treatments were self-reported and not verified through medical records. Nevertheless, side effects were gathered as general item of the diary but a more precise data acquisition could have been planned. Eventually, no systematic and periodic data collection on the quality and nature of sham treatment perceived by the patient was planned.

Comparing the present trial with other research published, the overall reduction in the number of days per month of migraine headache is similar to that reported in the osteopathic literature,[17,19,28] although much larger in terms of estimated clinical effects. The only other trial that enrolled migraineurs was conducted by Voigt et al.[17] The authors recruited only female migraine patients, including non-chronic subjects, whilst the present trial aimed to enrol a wider population focusing on chronic patients. Differences in osteopathic treatment applied have to be pointed out. Voigt et al. scheduled 5 fortnightly sessions over a 10-week treatment period using any type of technique compared to 8 treatments in 24 weeks utilizing indirect techniques only for the current research. Several other dissimilarities have to be highlighted in terms of primary outcomes measurement tools (MIDAS questionnaire vs HIT-6), study design (2-armed vs 3-armed) and type of statistical analysis used (univariate vs multivariate). Although sample and methodological differences, both studies demonstrated a decrease in pain, disability scores and increase in quality of life.

Speculating on the possible mechanism of action of OMT, two hypotheses could be considered: the rebalance of VNS and the reduction of pro-inflammatory substances. Migraine was demonstrated to be associated with functional alteration of both VNS[29–35] and specific autonomic nuclei responsible of pain perception and sustained pain.[6,14,36] If long-lasting, migraine may produce peripheral and central

sensitization as well as lack of habituation,[8,37,38] all phenomena which belong to the so-called ''pain-matrix''.[38]

Moreover, the underpinning dysautomonia condition was showed to reduce the release of norepinephrine and to increase the secretion of dopamine and prostaglandins.[35] In addition, during migraine attacks, high level of pro-inflammatory substances and serotonin is released[8,14] altering neural autonomic pathways.[13,16]

The application of OMT was demonstrated to influence the VNS, producing a parasympathetic effect[39,40] and leading, therefore, toward a trophotropic tuning state. Moreover, OMT seems to be associated with a reduction of pro-inflammatory substances both in vitro[41] and in vivo,[42,43] hypothesizing an anti-inflammatory role of OMT. Therefore the application of osteopathic manipulation in migraineurs could, possibly, reduce the release of pro-inflammatory substances, that in turn have an effect on the VNS function. As a consequence, a cascade of biological and neurological events, potentially based on a rebalance of the abnormal activation of the habituation/sensitization mechanism, even between attacks, could occur resulting in an overall improvement of clinical outcomes.

Considering the sham effect, it seems to be more prevalent and clinical effective during the first 3 months.

Although remains still partially unclear the mechanisms of action of impure placebos, possible speculations may arise to explain the effect of sham treatments. Several hypotheses were suggested, going from nonspecific psychological effect[44] to neurophenomenological model[45] to neurological theory.[46,47] However, the paucity and heterogeneity of findings prevent any defined theorization. Nevertheless, speculating on the potential mechanism of action of sham osteopathic treatment compared to control in adults, it is possible to consider expectation, reward and recovery as central neuro-psyco-biological aspects of positive clinical outcomes.[48,49] Arguably the prefrontal cortex and the limbic system play an important role in expectation and seem to be associated with pain control as well as with cognitive representation.[46,50,51] Soft touch, that is the essential nature of sham osteopathic treatment, was showed to induce responses at different levels of central nervous system associated with pain[52] as well as being one of the major influencing factor on interpersonal daily social life.[53] Based on this evidence, it could be possible to hypothesize a positive effect of sham procedure on adult migraineurs. In addition, results from the present trials showed a significant effect of sham treatment during the first 3 months. Although a dose-effect and time-effect mechanisms could be hypothesized, it remained largely unclear and scientifically unexplained any underpinning mechanism. Therefore, this serendipity and hedonic responses resulted from soft touch sham treatment may produce expectation for future benefit due to the reduction of the ''demoralization'',[54] leading to medium-term clinical benefits.

Several insights may be suggested in terms of health care policy. The use of osteopathy as an adjuvant therapy for migraine patients may reduce the use of drugs and optimize the clinical management of the patients. This could be considered by stakeholders and policy-makers in terms of improvement of health care policies and services. To further confirm these hypotheses, additional studies should address the economical value of the osteopathic treatment, changes in DALYs, QALYs and working days lost to allow a more adequate interpretation of health care impact. Surely larger and multicenter randomized trial including a wait-list control group and/or comparing different types of manual therapies would be appropriate to test the generalizability and external validity of these findings.

Conclusion

The present study showed significant differences between OMT group compared to drug and sham groups, suggesting that OMT may be considered a clinically valid procedure for the management of patients with migraine.

Conflict of interest statement

All authors declare no conflict of interests in regards with the present trial.

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