Accepted Manuscript

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PII: S1529-9430(16)30849-X
DOI: http://dx.doi.org/doi: 10.1016/j.spinee.2016.08.008
Reference: SPINEE 57124

To appear in: *The Spine Journal*

Received date: 11-3-2016
Revised date: 3-6-2016
Accepted date: 2-8-2016

Please cite this article as: Sureeporn Uthaikhup, Jenjira Assapun, Kanokwan Watcharasaksilp, Gwendolen Jull, Effectiveness of physiotherapy for seniors with recurrent headaches associated with neck pain and dysfunction: a randomized controlled trial, *The Spine Journal* (2016), http://dx.doi.org/doi: 10.1016/j.spinee.2016.08.008.

Effectiveness of physiotherapy for seniors with recurrent headaches associated with neck pain and dysfunction: a randomized controlled trial

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Acknowledgements

This trial was granted by the Thailand Research Fund (TRF), grant number: 5580145.

ABSTRACT

BACKGROUND CONTEXT: A previous study demonstrated that in seniors, the presence of cervical musculoskeletal impairment was not specific to cervicogenic headache but was present in various recurrent headache types. Physiotherapy treatment is indicated in those seniors diagnosed with cervicogenic headache but could also be adjunct treatment for those with cervical musculoskeletal signs who are suspected of having transitional headaches.

PURPOSE: To determine the effectiveness of a physiotherapy program for seniors with recurrent headaches associated with neck pain and cervical musculoskeletal dysfunction, irrespective of the headache classification.

STUDY DESIGN: Prospective, stratified, randomized controlled trial with blinded outcome assessment.

PATIENT SAMPLE: Sixty-five participants with recurrent headache, aged 50-75 years were randomly assigned to either a physiotherapy (n =33) or usual care group (n = 32).

OUTCOME MEASURES: The primary outcome was headache frequency. Secondary outcomes were headache intensity and duration, neck pain and disability, cervical range of motion, quality of life, participant satisfaction and medication intake.

METHODS: Participants in the physiotherapy group received 14 treatment sessions. Participants in the usual care group continued with their usual care. Outcome measures were recorded at baseline, 11 weeks, 6 months and 9 months. This study was funded by a government research fund of $6850. No conflict of interest is declared.

RESULTS: There was no loss to follow-up for the primary outcome measure. Compared to usual care, participants receiving physiotherapy reported significant reductions in headache frequency immediately after treatment (mean difference -1.6 days, 95% CI -2.5 to -0.6), at the

6-month follow-up (-1.7 days, 95% CI -2.6 to -0.8), at the 9-month follow-up (-2.4 days, 95% CI -3.2 to -1.5) and significant improvements in all secondary outcomes immediately post-treatment and at the 6- and 9-month follow-ups, ($p < 0.05$ for all). No adverse events were reported.

CONCLUSION: Physiotherapy treatment provided benefits over usual care for seniors with recurrent headache associated with neck pain and dysfunction.

KEY WORDS: cervical disorder, headache, neck pain, physiotherapy, seniors

Introduction

Headache is a common health problem that affects quality of life. Headaches change with age [1-3]. Their features become less typical, for example, a diagnosis of probable migraine is more prevalent in seniors than migraine [4]. Secondary headaches increase in frequency [5] and associated neck pain is common [2]. In line with this occurrence, we demonstrated that cervical musculoskeletal dysfunction (CMD) was more prevalent in seniors with, than without headache. CMD was not specific to cervicogenic headache but was present in various recurrent headache types (e.g. migraine, tension-type headache) [6]. Nevertheless, the degree of CMD was variable. We characterised it as greater or lesser based principally on loss of motion and pain on palpation of cervical joints. We found that greater or lesser dysfunction likewise was not related to headache classification or length of headache history, albeit that there was a trend for more cervicogenic headaches to be in the group with greater neck dysfunction. The CMD and neck pain in seniors might be the source of headache (cervicogenic headache), or a prevalent co-morbid feature and possibly an additional peripheral source of nociception in primary headaches as part of their changing nature with ageing.

Changes in the nature of headache with age play an important role in the choice of treatment. The effective management of headache in seniors remains a challenge. There is evidence that physiotherapy methods are effective for treating the CMD of cervicogenic headache [7, 8]. It is unknown if management of the neck could be a useful adjunct treatment for those seniors with other recurrent headaches as probable migraine when they are associated with neck pain and CMD. This is a safe option given the widespread concerns about medication overuse, adverse drug events and drug interactions in senior populations [9, 10]. Management of CMD may reduce headache frequency or severity, enhance the quality of life, and lessen medication use, cost and adverse drug events.

This trial was undertaken to determine the effectiveness of a physiotherapy program of cervical mobilization and therapeutic exercise for seniors with recurrent headache irrespective of headache classification, provided there was associated with neck pain and CMD. We hypothesized that treatment of the neck disorder would be more effective in reducing headache frequency than usual care and as secondary outcomes, would result in greater improvements in headache duration and intensity, cervical range of motion, neck pain and disability, medication use, quality of life and participant's perception of treatment benefit. If treatment of the neck proved effective, we planned subgroup analyses to determine if there was a difference in effect if the headache was diagnosed as cervicogenic or whether greater or lesser musculoskeletal dysfunction was judged to be present.

Methods

Study design

A prospective, assessor-blinded, parallel group (1:1 allocation ratio) randomized controlled trial. Ethical approval was gained from the ethical review committee for research in humans, Faculty of Medicine, Chiang Mai University (#349/2012). The study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. (ClinicalTrial.gov NCT01736774).

Participants

Participants were recruited both from the headache clinic at Maharaj University Hospital and from the local community by advertising on local radio, in newspapers and flyers. A neurologist from the headache clinic screened and diagnosed potential participants from both sources. To be eligible for the study, participants were to be aged between 50-75 years, have

recurrent headaches diagnosed as either migraine, tension-type, cervicogenic or mixed headache with associated neck pain and CMD (restriction in active range of cervical motion in extension and rotation and palpable upper cervical joint dysfunction) [6]. Headache frequency had to be at least one per week over the past year, neck ≥ 3 on a 0-10 visual analogue scale (VAS) and neck disability ≥ 10 out of 100 as measured by the Neck Disability Index (NDI). Exclusion criteria were: headache diagnosed as temporal arteritis, trigeminal neuralgia, cluster headache, chronic paroxysmal hemicrania/hemicranias continua; temporomandibular disorders; neurological disorders (e.g. Parkinson disease, stroke); cognitive disturbance; previous serious head and neck trauma; any condition that contraindicated cervical mobilization; or receipt of physiotherapy treatment for headache during the past 12 months.

A research assistant conducted a preliminary screening telephone interview with participants responding to advertisements. For those provisionally eligible for the trial, appointments were made with the trial neurologist and an experienced physiotherapist. The neurologist examined all potential participants (recruited from advertisements or the headache clinic) and assigned a headache diagnosis (migraine, tension-type, cervicogenic, mixed headache or other headache type) according to the criteria of the International Headache Society (IHS) [11] or for cervicogenic headache, the criteria of the Cervicogenic Headache International Study Group [12]. The physiotherapist, blinded to the neurologist's diagnosis, performed a physical examination of the neck to identify the presence or not of CMD and make the clinical rating of greater, lesser or no CMD [6]. This included assessment of range of movement and a manual examination of the cervical segments [13, 14]. The participants rated any pain provoked on palpation on a numerical rating scale (NRS) and the physiotherapist rated the perceived tissue resistance to the manual palpation as normal, slight, moderate, or marked resistance. A joint was classified as symptomatic if pain provoked by manual examination was >2/10 in

combination with the physiotherapist's rating of moderately or markedly abnormal tissue compliance [15]. A participant was judged to have greater CMD if they had at least 2 levels of symptomatic joint dysfunction and displayed restricted range of cervical motion in extension and rotation. If musculoskeletal dysfunction was present, but rated to lesser degree, the participant was assigned to lesser CMD. If manual examination and range of movement were painfree, a participant was assigned to have no CMD. On the basis of the neurologist's and physiotherapist's assessments, participants were either invited to participate or were judged ineligible.

Randomization and masking

Randomization was undertaken by an independent research assistant, not otherwise involved in the trial. Randomization was by computer generated permuted blocks with a block size of four, stratified by greater or lesser CMD, to ensure similar dysfunction between groups. Allocation was concealed in sequentially numbered, sealed, opaque envelopes. The envelopes were opened by the research assistant allocating patients to the respective intervention. Physiotherapists were not blinded to the treatment being provided but were blinded to participants' headache diagnosis. Blinded assessors collected all baseline and follow-up physical measures and entered questionnaire data.

Interventions

Physiotherapy: The intervention was delivered by two physiotherapists, experienced in the trial treatments. The treatment period was 10-weeks and commenced within one week of baseline assessment. Participants received 14 individual treatment sessions (2 visits per week for the first 4 weeks followed by one visit per week for the last 6 weeks). Each treatment session lasted approximately 45 minutes and included a combination of cervical mobilization and a

therapeutic exercise program, a regime which has proven successful in previous trials of headache management [7, 16]. The cervical mobilization consisted of low-velocity techniques [17]. The therapeutic exercise program was a low load exercise for the craniocervical flexor [7, 18] and axioscapular muscles [19] and postural correction exercises [18, 20]. Muscle lengthening exercise could also be given to address any muscle tightness. The elements of the treatment were delivered at the discretion of the physiotherapist, based on the initial and progressive assessment of participant's cervical joint and muscular dysfunction. The exercise programs were progressed gradually from non-functional to functional performance. Participants were instructed to practice their exercise once daily (10-20 minutes) during the intervention period, without aggravating pain. Participants completed an exercise diary to monitor compliance and record adverse events. Significant adverse effects were defined as any increases in pain (headache or neck pain), loss of neck motion, and/or loss of function as a result of the intervention.

Usual care: Participants randomly allocated to the usual care group were asked to continue with their medication and were able to receive other care as they thought appropriate except for physiotherapy treatment. To avoid the risks of behavioral change, the usual care group received only neutral information. No extra information about their condition or treatment advice was provided. Any treatments received and adverse events during the 10 week intervention period were recorded in a diary log-book.

Measurements

A baseline questionnaire was administered to document participant demographics, headache history and any treatment received to date. A daily headache diary was used to record headache measures (frequency, intensity and duration) one week before baseline and follow-up

assessments. Primary and secondary outcome measures were recorded at baseline, 11 weeks, 6 months and 9 months after randomization. The exception was cervical range of motion, participants' perception of treatment benefit and quality of life which were measured at baseline, 11 weeks and 9 months.

Primary outcome measure

Headache frequency was the primary outcome measure [21]. The number of headache days was recorded in a daily headache diary one week before the respective assessment dates and the total number of headache days per week was used for analysis.

Secondary outcome measures

Other headache measures: Headache intensity and duration were measured with a daily headache diary. Participants reported daily headache pain intensity using a 0-10 NRS and the number of hours of headache for each day in the past week. Means scores across the 7-day period were used for analysis.

Neck pain and disability measures: Neck pain intensity was measured using a VAS. The participants indicated their average neck pain intensity over the past week by marking a 100mm line. Likewise a weekly measure was recorded of neck related disability using the Neck Disability Index-Thai version (NDI-TH) [22]. The NDI-TH has 10 sections and each has a five point Likert response (total score, 50). A higher score indicates greater perceived disability [23].

Cervical range of motion: A cervical range of motion (CROM) device was used to measure flexion/extension, left-right rotation, left-right lateral flexion and left-right upper cervical rotation [24]. The CROM is a reliable tool to assess cervical range of motion [25].

Quality of life: Health-related quality of life was assessed using the SF-36-Thai version [26], which contains 36 questions covering eight domains of health. The eight domains were summed into a physical component summary score (PCS) and a mental component summary score (MCS) and then expressed as a percentage, with higher score representing better health.

Participant's perception of treatment benefit: Perceived benefit was measured with a 0-10 scale (0 = no benefit and 10 = maximum benefit).

Medication: Participants recorded the type and dose of all medications taken in a medication diary for a one-week baseline period and for one week prior to follow-up points. Medication consumption was converted into defined daily dose (DDD) unit by multiplying the units dispensed field with the DDD conversion [27]. For example, the DDD for paracetamol is 3g and the strength of one tablet is 500mg. Each 500mg tablet is equivalent to 0.17 DDD. Multiplying the quantity (6 tablets) by a conversion factor of 0.17 equals a consumption of 1.02 DDDs. The sum of DDDs of all medications consumed in one week was calculated and used for analysis.

Procedure

Participants attended the Department of Physiotherapy, Chiang Mai University for baseline assessment. They were randomly allocated to either the 10 week physiotherapy program or usual care. All participants were reassessed at 11 weeks (at the university), 6 months (postal questionnaires) and 9 months (at the university). All participants were asked to complete a daily headache diary for the week before each re-assessment date. They noted the presence or not of headache on each day, its intensity and duration and also whether it was their familiar headache or a different headache, for example, associated with a cold or flu. Participants

receiving the physiotherapy intervention were asked to refrain from seeking other treatment for their headache during the trial. Due to ethical considerations, usual medication was not withheld from any participant, regardless of group. Participants recorded the type and dose of all medications taken in a medication diary. Reminder telephone calls were used to help to maintain a high retention rate, including two calls to participants in the usual care group during the 10 week intervention.

Sample size calculation

Sample size was based on the primary outcome of headache days per week. According to the IHS guidelines [21], a 50% reduction in headache days per week is considered a clinically significant difference. A sample size of 58 participants was required for the study based on a priori power analysis with a power of 0.8 and an alpha of 0.05. Assuming a dropout rate of 10%, 64 participants (32 per group) was the target sample size for enrollment.

Statistical analysis

Independent t-tests and Chi-square analyses were performed to compare demographic characteristics between participants and people who refused to participate. Imputation method was used for handling missing data, which occurred in one participant in the physiotherapy group for cervical movement at the 9-month follow-up due to lack of time. Two analytic approaches (the last observation carried forward and likewise deletion) were applied in a preliminarily analysis to inform the handling of single missing data at random. Similar outcomes were obtained. Missing data imputation by the last observation carried forward was chosen to minimize the number of the participant eliminated from analysis. The change from baseline (mean and 95% confidence interval) for each pairwise between-group comparison and within groups was estimated using a linear mixed model with Bonferroni post-hoc adjustment

and the baseline value was used as a covariate. A partial eta squared (η2) was calculated to determine effect size. An effect size of 0.01 was regarded as small, 0.06 as medium, and 0.14 as large [28]. Dichotomous responder analysis was conducted to evaluate whether improvement in headache frequency was clinically significant (≥ 50% reduction in the number of headache days post-treatment and at follow-ups). The results are presented as relative risks with 95% confidence interval.

Subgroup analyses were explored to determine whether any effects of neck treatment differed according to headache diagnosis (cervicogenic or non-cervicogenic) or CMD (greater or lesser). Analyses were performed based on tests for the 3-way interaction between each subgroup (headache diagnosis or musculoskeletal dysfunction), treatment allocation (physiotherapy and usual care), and time (11 weeks, 6 months and 9 months). No interaction would indicate similar treatment effects in subgroups over time [29]. Differences in demographic and baseline data between groups (cervicogenic versus non-cervicogenic, and greater versus lesser CMD) were initially tested using independent-t test and chi-square. Significant differences were evident in age and baseline data (headache frequency, intensity and duration, and neck pain intensity and disability) between the groups. Age and baseline data were then adjusted in the 3-way interaction analyses. Subgroup analyses were confined to the primary outcome (headache frequency) and key secondary outcomes (headache intensity and duration, and neck pain and disability).

Statistical significance was set at $p < 0.05$. Data were analyzed using SPSS Statistics version 18 (SPSS Co., Ltd. Bangkok, Thailand).

Results

Participant characteristics

The study commenced in January 2013 and was completed in July 2015. Figure 1 presents the flow diagram of participant recruitment and retention. Sixty-five participants entered the study and none were lost to follow-up for the primary outcome. Data for cervical movement was not collected from one participant (3%) in the physiotherapy group at the 9-month follow-up. Demographic characteristics between participants and persons who refused to join the trial are presented in Table 1. Fifteen people who refused passed the preliminary screening but declined diagnostic and physical assessments for headache. No significant differences in demographic characteristics were found between participants and persons who refused to participate ($p > 0.05$)

Interventions

All participants in the physiotherapy group completed 14 treatment sessions over 10 weeks. Analysis of exercise diaries indicated that participants practiced exercises on 63.4 (SD, 8.7) of 70 days of the treatment period. Three participants in the usual care group reported using balm to reduce pain, six received massage, and one received acupuncture. Four participants in the treatment group reported discomfort around their neck after the first treatment and the discomfort disappeared within 24 hours. No significant adverse effects were reported in either group.

Primary outcome

Descriptive data for the primary outcome from baseline to each follow period are summarized in Table 2 and results of analysis of changes between and within-groups are presented in Table 3. The participants receiving physiotherapy had significantly reduced headache frequency immediately after treatment (week 11) compared with usual care. The difference remained

significant at 6- and 9-month follow-ups. Effect size estimates indicated a large effect for physiotherapy treatment on headache frequency (Table 4). The effectiveness of the intervention was also investigated by examining the number of participants who responded to treatment. At all follow up points, the physiotherapy group had a significantly higher proportion of participants who experienced greater than 50% reduction in headache frequency than the usual care group and 60% were headache free at 9-months (Table 5).

Secondary outcomes

Descriptive data for secondary outcomes at each time point are summarized in Table 2. Results of analysis of changes between and within-groups are presented in Table 3. There were significant reductions in headache intensity and duration, neck pain and disability measures (VAS and NDI-TH) immediately after treatment (11 weeks), and at 6- and 9-month time points compared to the usual care group. Significant differences between groups were recorded at the post-treatment (11 weeks) and the 9 month follow-up, for cervical ranges of motion, quality of life measures and participant's perception of treatment benefit. The exception was upper cervical rotation at the 9 month follow up. There was a positive trend for reduced medication use in the physiotherapy group, but differences from the usual care group were not significant.

Subgroup analyses

Descriptive data for subgroup analyses are present in Tables 6 and 7. Cervicogenic headache was the most common diagnosis (69.7%, physiotherapy group; 65.6%, usual care group) and, for analysis, all other headaches were pooled into a non-cervicogenic headache group. Approximately 75% of participants in each group were rated with greater CMD. After adjusting for age and baseline data, there were no interactions between subgroups (headache diagnosis and CMD) and treatment allocation over time for the primary outcome and

secondary outcomes (headache intensity and duration; neck pain and disability measures ($p > 0.05$). The exception was headache duration, where a significant interaction was found between subgroup of CMD, treatment allocation and time ($p = 0.012$). Bonferroni post-hoc results showed that post-treatment (11 weeks), participants with greater CMD in the physiotherapy group had significantly greater improvement in headache duration than those with lesser CMD (mean difference = 3.3 hours/day, 95% CI = 0.3 to 6.3, $p = 0.031$).

Discussion

In older age, primary headaches as migraine become less typical, secondary headaches increase in frequency and neck pain with headache is prevalent [2, 4, 5]. We included participants with diagnoses of migraine, tension-type, mixed or cervicogenic headache. Nevertheless, our primary inclusion criteria were the presence of neck pain and CMD for which there is evidence of effectiveness of the physiotherapy interventions used in this study [7, 16]. This study demonstrated that a treatment program consisting of cervical mobilization and therapeutic exercise significantly reduced headache frequency in seniors with recurrent headache compared with usual care. Greater improvement also occurred in headache intensity and duration, neck pain intensity and disability, range of motion and quality of life. Participants perceived treatment as beneficial. Additionally, there was a trend for reduction in average daily medication dose in the physiotherapy group. Treatment effects were evident immediately after treatment and were maintained in the long-term. No noteworthy adverse effects were reported. Taken together, the results indicate that conservative physiotherapy management of the neck is a suitable intervention for seniors with recurrent headache associated with neck pain and CMD.

Estimates of effect size were large for most headache symptoms at week 11, and at 6 and 9 months. In clinical terms, treating the neck was approximately twice as effective as usual care

in achieving a clinically relevant reduction in headache frequency (>50% reduction) and approximately 60% reported complete relief from headache with neck treatment compared to 28% in the usual care group at the long term follow-up. Notably, two-thirds of seniors were diagnosed with cervicogenic headache, and of the remainder, migraine was diagnosed most commonly (60%). This may reflect our inclusion criteria of the presence of neck pain and CMD and the purported greater prevalence of cervicogenic headache after the age of 50 [30, 31]. Additionally, with strict eligibility criteria to maintain internal validity, only one-third of seniors with headache were included in the trial. Thus the trial findings may have limited generalizability.

Other studies have also demonstrated effectiveness of cervical mobilization and therapeutic exercise for patients with cervicogenic headache [7, 8]. Interestingly, the sub-group analyses revealed that our clinical estimate of magnitude of CMD (lesser or greater) did not impact on the chance of a favorable outcome and notably there was no difference in treatment effects according to headache classification (cervicogenic or non-cervicogenic). We make no general claim that treatment of the neck is efficacious for non-cervicogenic headaches as migraine. Neck pain may be an expression of the centrally sensitized trigemino-cervical nucleus [32] rather than signal a local cervical disorder. Indeed, a systematic review in 2011 concluded that there was no support for the use of spinal manipulations in treatment for migraine [33]. Likewise, a recent study investigating the effect on migraine of medication alone or combined with physiotherapy (cervical mobilization and muscle stretching) found marginal but no significant additional benefit of physiotherapy on headache frequency [34].

These findings seem at variance to the results of our study where the diagnosis of migraine in some participants did not mitigate against benefit from the physiotherapy intervention.

Interestingly in the previous migraine trial [34], there was no improvement in cervical range of motion. An improvement could be expected with such treatment if any neck pain was related to CMD. Our participants, receiving similar physiotherapy interventions showed improvements in range of movement in excess of the minimal clinically important difference (6.5° in any direction) [25] and achieved clinically meaningful change (≥20%) in the NDI score [35]. The difference in our cohort was that, regardless of headache diagnosis, they were required to have CMD in association with headache and any associated neck pain. The outcomes of our trial would suggest that this CMD played an active role in headache. Our results provide evidence that cervicogenic headache in seniors is responsive to local treatment of the neck. The results also suggest that neck pain associated with CMD could be an additional peripheral source of nociception in primary headache in seniors, which is responsive to local treatment of the neck. The study highlights the importance of offering a pragmatic approach for management of seniors who experience recurrent headache in association with neck pain and CMD.

There are limitations to this trial. Blinding of the treating physiotherapists and participants was not possible. Performance bias, that is, participants allocated to the treatment group received more attention during the 10 week intervention period, may contribute to a greater chance of positive outcomes. Participant selection was based on classification criteria for migraine, tension-type [11] and cervicogenic headache [12], but diagnostic nerve or joint blocks to confirm cervicogenic headache could not be justified for our cohort of seniors. The headache diary entries were not electronically time-stamped. Some participants may have backfilled their diaries, resulting in recall issues. The sample size was not justified for the subgroup analyses. The subgroup analyses represented a relatively small number of participants and results should be interpreted with some caution, although results were non-significant.

Conclusions

A program of low-velocity cervical mobilization and therapeutic exercise is effective for seniors with recurrent headache when associated with neck pain and CMD, regardless of headache classification. Given the heterogeneity of headache in this age group, concerns about medication overuse and drug interactions, management of any associated painful CMD might contribute positively to a multifactorial headache intervention strategy for this group.

Conflict of Interest Statement

There is no conflict of interest.

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Figure 1 Flow diagram of the trial

Table 1 Demographic characteristics between participants and persons who refused to participate

Variables	Participants			Refusers (n =24)	p-value**
	Physiotherapy (n = 33)	Usual care (n = 32)	Total (n =65)		
Age (yrs), mean (SEM)	59.9 (1.2)	61.6 (0.9)	60.7 (0.7)	63.2 (1.4)	0.10
Gender (female), %	81.8	90.6	86.2	87.5	0.87
BMI (kg/m^2), mean (SEM)	24.1 (0.7)	25.8 (0.6)	24.9 (0.5)	26.6 (0.9)*	0.22
Employment status, n					
Retired	7	8		-	-
Full time employment	9	3		-	-
Self-employed	10	16		-	-
Housewife	7	5		-	-
History of headache (yrs), mean (SEM)	8.5 (1.6)	6.3 (1.5)	7.4 (1.1)	3.9 (1.1)	0.07
Headache diagnosis (type), n					0.58
Migraine	6	7	13	1*	
Tension-type headache	2	0	2	0	
Cervicogenic headache	23	21	44	8*	
Mixed headache	2	4	6	0	
CMD (greater), %	75.8	75.0	75.4	55.6*	0.21

CMD = cervical musculoskeletal impairment

* Total number of refusers (n = 9)

** Compared between refusers and total participants

Table 2 Primary and secondary outcomes for each intervention group. Means and (standard deviations) are presented.

Outcome variables	Physiotherapy (n = 33)				Usual care (n = 32)			
	Baseline	11 weeks	6 months	9 months	Baseline	11 weeks	6 months	9 months
Primary outcome								
Headache frequency (days/week)	4.3 (0.4)	1.7 (0.4)	1.5 (0.4)	0.8 (0.2)	3.9 (0.4)	3.0 (0.4)	2.9 (0.5)	2.9 (0.5)
Secondary outcome								
Headache intensity (0-10 NRS)	4.5 (0.3)	1.4 (0.3)	1.5 (0.3)	1.2 (0.3)	4.7 (0.4)	4.8 (0.4)	4.0 (0.5)	3.6 (0.6)
Headache duration (hours/day)	5.2 (1.0)	2.2 (0.6)	2.7 (0.9)	1.9 (0.9)	4.8 (1.0)	4.7 (1.0)	4.7 (1.1)	5.60 (1.2)
Neck pain intensity (0-10 VAS)	5.1 (0.3)	1.7 (0.2)	1.4 (0.3)	1.5 (0.3)	5.4 (0.2)	4.73 (0.2)	4.8 (0.3)	4.80 (0.3)
Neck pain and disability (%)	30.9 (1.6)	10.1 (1.2)	9.2 (1.3)	8.4 (1.3)	27.7 (1.7)	26.4 (1.5)	24.6 (1.6)	23.83 (1.8)
Cervical range of motion (degrees)								
Flexion-extension	105.0 (1.6)	115.6 (1.9)	N/A	113.0 (1.7)	105.5 (1.8)	105.9 (1.6)	N/A	107.23 (2.5)
Lateral flexion (right-left)	58.5 (2.0)	66.3 (2.1)	N/A	68.1 (2.1)	59.7 (1.6)	59.9 (1.5)	N/A	64.6 (1.7)

Outcome variables	Physiotherapy (n = 33)				Usual care (n = 32)			
	Baseline	11 weeks	6 months	9 months	Baseline	11 weeks	6 months	9 months
Rotation (right-left)	115.2 (2.2)	125.0 (1.9)	N/A	125.2 (2.1)	115.1 (2.0)	115.5 (2.4)	N/A	117.9 (1.9)
Upper cervical rotation	47.7 (1.1)	53.3 (1.0)	N/A	53.6 (1.2)	49.0 (0.9)	51.0 (1.0)	N/A	51.7 (1.0)
Quality of life SF 36 (%)								
Physical component summary	54.5 (2.6)	78.4 (2.0)	N/A	77.7 (2.1)	55.7 (2.8)	53.6 (2.7)	N/A	56.6 (2.2)
Mental component summary	65.6 (2.8)	83.7 (1.9)	N/A	79.4 (2.4)	68.8 (2.7)	62.1 (3.0)	N/A	63.2 (3.0)
Treatment benefit (0-10 VAS)	4.5 (0.6)	9.3 (0.2)	N/A	9.4 (0.2)	3.6 (0.6)	6.3 (0.5)	N/A	6.7 (0.4)
Medication (DDD per week)	2.0 (1.5)	0.04 (0.02)	0.05 (0.04)	0.03 (0.02)	0.7 (0.3)	1.2 (0.8)	1.0 (0.8)	1.3 (0.8)

Data are expressed in mean (standard error), NRS = Numerical Rating Scale, VAS = Visual Analogue Scale, DDD = Defined Daily Dose

Table 3 Means (standard error) for within group changes and adjusted mean (95% confidence interval) for differences in between-group change for all outcome variables

Outcome variables	Time frame	Change within groups*				Changes between-groups**	
		Physiotherapy	*p*-value	Usual care	p-value	Difference	p-value
Primary outcome							
Headache frequency (days/week)	Baseline-week 11	2.6 (0.3)	<0.001	0.9 (0.4)	0.052	-1.6 (-2.5 to -0.6)	0.001
	Baseline-6 months	2.8 (0.4)	<0.001	1.0 (0.4)	0.041	-1.7 (-2.6 to -0.8)	0.001
	Baseline-9 months	3.5 (0.3)	<0.001	1.0 (0.3)	0.023	-2.4 (-3.2 to -1.5)	<0.001
Secondary outcomes							
Headache intensity (0-10 NRS)	Baseline-week 11	3.1 (0.3)	<0.001	-0.1 (0.3)	1.00	-3.3 (-4.1 to -2.4)	<0.001
	Baseline-6 months	2.9 (0.4)	<0.001	0.7 (0.4)	0.49	-2.3 (-3.4 to -1.3)	<0.001
	Baseline-9 months	3.2 (0.5)	<0.001	1.1 (0.5)	0.32	-2.4 (-3.6 to -1.1)	<0.001
Headache duration (hours/day)	Baseline-week 11	3.0 (0.8)	0.005	0.2 (0.9)	1.00	-2.6 (-4.4 to -0.7)	0.007
	Baseline-6 months	2.5 (0.8)	0.020	0.2 (0.8)	1.00	-2.2 (-4.4 to -0.04)	0.046
	Baseline-9 months	3.3 (1.2)	0.033	-0.8 (1.2)	1.00	-3.8 (-6.6 to -1.0)	0.008

Outcome variables	Time frame	Change within groups*				Changes between-groups**	
		Physiotherapy	*p*-value	Usual care	p-value	Difference	p-value
Neck pain intensity (0-10 VAS)	Baseline-week 11	3.5 (0.3)	<0.001	0.7 (0.3)	0.18	-3.0 (-3.7 to -2.4)	<0.001
	Baseline-6 months	3.7 (0.3)	<0.001	0.6 (0.3)	0.58	-3.3 (-4.1 to -2.6)	<0.001
	Baseline-9 months	3.7 (0.3)	<0.001	0.6 (0.3)	0.59	-3.3 (-4.1 to -2.4)	<0.001
Neck pain and disability (%)	Baseline-week 11	20.8 (1.5)	<0.001	1.3 (1.5)	1.00	-17.7 (-21.1 to -14.2)	<0.001
	Baseline-6 months	21.7 (1.7)	<0.001	3.1 (1.7)	0.49	-16.5 (-20.4 to -12.6)	<0.001
	Baseline-9 months	22.5 (1.8)	<0.001	3.9 (1.9)	0.26	-16.4 (-20.6 to -12.2)	<0.001
Cervical range of motion (degrees)							
Flexion-extension	Baseline-week 11	-10.6 (1.5)	<0.001	-0.5 (1.6)	1.00	10.0 (6.0 to 14.0)	<0.001
	Baseline-9 months	-8.1 (1.7)	<0.001	-1.8 (1.7)	0.91	6.19 (1.5 to 10.9)	0.010
Lateral flexion (right-left)	Baseline-week 11	-7.9 (1.6)	<0.001	-0.3 (1.7)	1.00	7.1 (3.0 to 11.3)	0.001
	Baseline-9 months	-9.6 (1.6)	<0.001	-4.9 (1.6)	0.01	4.3 (0.2 to 8.5)	0.043
Rotation (right-left)	Baseline-week 11	-9.8 (1.8)	<0.001	-0.3 (1.8)	1.00	9.5 (4.8 to 14.2)	<0.001
	Baseline-9 months	-10.0 (1.9)	<0.001	-2.8 (1.9)	0.48	7.3 (2.6 to 12.0)	0.003

Outcome variables	Time frame	Change within groups*				Changes between-groups**	
		Physiotherapy	*p*-value	Usual care	p-value	Difference	p-value
Upper cervical rotation	Baseline-week 11	-5.6 (1.2)	<0.001	-1.9 (1.2)	0.30	2.8 (0.1 to 5.5)	0.045
	Baseline-9 months	-5.9 (1.2)	<0.001	-2.7 (1.2)	0.10	2.4 (-0.6 to 5.4)	0.11
Quality of life SF 36 (%)							
Physical component summary	Baseline-week 11	-24.0 (2.7)	<0.001	2.1 (2.7)	1.00	25.3 (19.2 to 31.4)	<0.001
	Baseline-9 months	-23.3 (2.6)	<0.001	-0.9 (2.7)	1.00	21.6 (16.0 to 27.2)	<0.001
Mental component summary	Baseline-week 11	-18.1 (2.3)	<0.001	6.7 (2.4)	0.019	23.4 (17.6 to 29.2)	<0.001
	Baseline-9 months	-13.8 (2.5)	<0.001	5.6 (2.6)	0.10	17.9 (11.6 to 24.2)	<0.001
Treatment benefit (0-10 VAS)	Baseline-week 11	-4.8 (0.7)	<0.001	-2.8 (0.7)	0.001	3.1 (2.1 to 4.1)	<0.001
	Baseline-9 months	-4.9 (0.7)	<0.001	-3.1 (0.7)	<0.001	2.8 (2.0 to 3.6)	<0.001
Medication (DDD per week)	Baseline-week 11	2.0 (1.1)	0.56	-0.5 (1.2)	1.00	-1.3 (-2.8 to 0.3)	0.10
	Baseline-6 months	1.9 (1.2)	0.57	-0.3 (1.2)	1.00	-1.1 (-2.6 to 0.5)	0.17
	Baseline-9 months	2.0 (1.2)	0.56	-0.6 (1.2)	1.00	-1.4 (-3.0 to 0.1)	0.073

** adjusted for baseline values

* For changes within groups, positive values denote improvement, except for cervical range of motion, SF 36 and treatment benefit where negative values denote improvement.

** For differences in changes between-groups, positive values in cervical range of motion, SF 36 and treatment benefit, and negative values in the headache characteristics, neck pain intensity, neck disability and medication favor the first named group (physiotherapy) in the pairwise comparison.

Table 4 Effect size estimates for group differences

Outcome	Effect size (η2p)		
	Baseline to after treatment	Baseline to 6 month-follow up	Baseline to 9 month-follow up
Headache frequency	0.16	0.17	0.35
Headache intensity	0.49	0.25	0.19
Headache duration	0.11	0.06	0.11

Table 5 The number of participants (%) with a greater than 50% and 100% reduction in headache frequency at follow-ups compared to baseline

	50% reduction				100% reduction			
Headache frequency	Physiotherapy n =33	Usual care n =32	p-value	Relative risk (95% confidence interval)	Physiotherapy n =33	Usual care n =32	p-value	Relative risk (95% confidence interval)
11 weeks	24 (72.7)	13 (40.6)	0.009	1.8 (1.1 to 2.9)	16 (48.5)	2 (6.3)	<0.001	7.8 (1.9 to 31.1)
6 months	27 (81.8)	15 (46.9)	0.003	1.8 (1.2 to 2.6)	15 (45.5)	7 (21.7)	0.045	2.1 (1.0 to 4.4)
9 months	31 (93.9)	14 (43.8)	<0.001	2.2 (1.4 to 3.2)	20 (60.6)	9 (28.1)	0.008	2.2 (1.2 to 4.0)

Table 6 Sub-group analyses based on cervicogenic or non-cervicogenic headache for the primary outcome and key secondary outcomes

Outcome variables	Physiotherapy		Usual care		p value for interaction treatment*sub-group*time
	Cervicogenic (n = 23)	Non-cervicogenic (n = 10)	Cervicogenic (n = 21)	Non-cervicogenic (n = 11)	
Primary outcome					
Headache frequency (days/week)	1.6 (0.6 to 2.5)	1.6 (0.3 to 3.0)	2.1 (1.0 to 3.1)	4.0 (2.8 to 5.2)	0.19
Secondary outcome					
Headache intensity (0-10 NRS)	2.1 (1.1 to 3.0)	1.5 (0.2 to 2.9)	3.7 (2.6 to 4.7)	4.7 (3.4 to 5.9)	0.079
Headache duration (hours/day)	3.4 (1.3 to 5.5)	0.6 (-2.4 to 3.6)	4.2 (1.8 to 6.6)	6.5 (3.7 to 9.3)	0.87
Neck pain intensity (0-10 VAS)	1.8 (1.3 to 2.3)	1.1 (0.3 to 1.8)	4.6 (4.0 to 5.1)	5.1 (4.4 to 5.9)	0.45
Neck pain and disability (%)	10.2 (7.8 to 12.7)	4.6 (1.0 to 8.3)	25.0 (22.4 to 27.6)	27.0 (23.5 to 30.5)	0.23

Value are estimated mean (95% confidence interval) after adjusting for baseline values and age

Table 7 Sub-group analyses based on greater or lesser musculoskeletal dysfunction for the primary outcome and key secondary outcomes

Outcome variables	Physiotherapy		Usual care		p value for interaction treatment*sub-group* time
	Greater dysfunction (n = 25)	Lesser dysfunction (n = 8)	Greater dysfunction (n = 24)	Lesser dysfunction (n = 8)	
Primary outcome					
Headache frequency (days/week)	1.1 (0.5 to 1.7)	1.2 (0.2 to 2.2)	3.1 (2.5 to 3.6)	3.1 (2.1 to 4.2)	0.15
Secondary outcome					
Headache intensity (0-10 NRS)	1.2 (0.6 to 1.8)	2.0 (0.9 to 3.1)	3.9 (3.3 to 4.5)	4.7 (3.6 to 5.7)	0.20
Headache duration (hours/day)	1.9 (0.4 to 3.4)	2.7 (0.01 to 5.3)	4.9 (3.4 to 6.4)	6.0 (3.3 to 8.7)	0.012
Neck pain intensity (0-10 VAS)	1.6 (1.1 to 2.1)	1.3 (0.5 to 2.2)	4.5 (4.0 to 5.0)	5.5 (4.6 to 6.4)	0.68
Neck pain and disability (%)	8.1 (5.6 to 10.5)	9.6 (5.3 to 13.8)	24.9 (22.5 to27.3)	28.5 (24.1 to 32.9)	0.71

Value are estimated mean (95% confidence interval) after adjusting for baseline values and age