Manual therapy as a prophylactic treatment for migraine. Design of a randomized controlled trial.

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Abstract

Background: People with migraine often experience disability with serious consequences for social life and work productivity. The effectiveness of pharmacological prophylactic management of migraine is limited, leading to a demand for non-pharmacological treatment options. We present the design and discuss the feasibility of a pragmatic, randomized controlled trial on the effectiveness of a multimodal manual therapy (MT) treatment compared to usual care by the general practitioner (GP) for the prophylactic treatment of migraine. Methods: Eligible participants will be recruited in primary care using the International Classification of Headache Disorders III criteria for migraine of the International Headache Society. Participants will be randomized to either multimodal MT treatment or usual care provided by the GP. GPs will be asked to treat the usual care group according to the Dutch GP guideline for headache. The multimodal MT intervention will include manual pressure techniques, neck muscle-strength exercises, and mobilization of the cervical and thoracic spine. The trial will consist of a 12 weeks treatment period and follow-up measurements at 12, 26 and 52 weeks. The primary outcome measure is the number of migraine days per four weeks, assessed with a headache diary. Secondary outcome measures are the number of migraine attacks, medication use, disability due to headache, headache intensity, number of participants reporting a 50% migraine reduction, measurement of cervical pressure pain thresholds, presence of allodynia, endurance of cervical flexor muscles, days of absence of work and global perceived effect. Discussion: The results of the trial will show if a multimodal MT intervention is an effective non-pharmacological treatment option for people with migraine. Trial registration: 7 February 2019 Dutch Trial Register (NL7504)

Background

Migraine is a common and often disabling disorder with a high impact on work, household and social life [1]. The 1-year prevalence of migraine is estimated at 15%, and migraine is ranked as the seventh-highest cause of disability in the Global Burden of Disease study [1][2]. In Europe, the total cost of migraine is estimated at 50 billion euro a year, making migraine the most costly headache disorder [3]. Therefore, effective treatments that reduce the frequency of migraine are highly needed [4]. The prophylactic management of migraine generally consists of pharmacological treatment [4]. Prophylactic medication (e.g., propranolol, topiramate or amitriptyline) reduces migraine attacks by 50% in 50% of the patients [5].

However, taking this medication has some disadvantages. Daily intake of prophylactic medication can cause side effects, such as fatigue and dizziness, which induce some patients to refuse this medication [6]. This has led to a growing demand for non-pharmacological prophylactic treatments to reduce the frequency of migraine [7].

The results of several studies in the last decades suggest that manual therapy (MT) might be an effective treatment to reduce migraine frequency and intensity [8]. However, these studies had small sample sizes and lacked appropriate randomization, allocation concealment, blinding, intention to treat analysis, and loss to follow-up [8]. Also, publication bias may have favored studies with positive results. If manual

therapy is an effective treatment for the reduction of migraine attacks, it may result in a reduction of the use of drugs, which have side effects, and in a reduction of impact on personal life. Therefore, rigorous, pragmatic research is needed that is in line with the International Headache Society (IHS) guidelines for controlled trials in migraine to determine the effectiveness of MT [9].

MT treatment for the management of headaches commonly consists of mobilization and manipulation of the cervical and thoracic spine in combination with specific exercises, posture corrections and myofascial soft tissue techniques [10][11][12]. A multimodal MT approach, including mobilization and manipulation of the cervical spine in combination with exercise, has been reported to be effective for tension-type headache [10][11][13].

The pathophysiological mechanism of migraine is still not fully understood, but sensitization of the trigemino-cervical complex has been suggested to play an important role [14][15][16] [17] [18]. Bartsch & Goadsby (2002) showed convergence of nociceptive afferent input by cervical dorsal roots of C1 to C3 and trigeminal afferent input onto second-order neurons at the trigemino-cervical complex [19]. This convergence of cervical and trigeminal nociception is supported by the frequent clinical presentation of people with migraine who also experience pain and allodynia in the cervical and cephalic region [20][21]. Manual pressure on cervical myofascial structures can provoke a typical migraine headache, indicating referred pain based on the convergence of cervical and ophthalmic nociceptive afferents at the trigemino-cervical complex [22][23].

Decreased pressure pain thresholds have been associated with sensitization. In migraine, decreased pressure pain thresholds of the upper cervical structures and the trapezius muscle are common [24][25]. Migraine is associated with cervical musculoskeletal dysfunction such as cervical myofascial trigger points, decreased endurance of the neck flexor muscles and restricted mobility of the upper cervical spine [23][26][27]. A combination of manual pressure techniques on myofascial trigger points, neck muscle strength exercises and mobilizations of the cervical and thoracic spine targets to decrease cervical nociceptive input and to reduce sensitization of the trigemino-cervical complex. We hypothesize that manual therapy can reduce the frequency of migraine by decreasing the nociceptive transmission in the trigemino-cervical complex.

The objective of our randomized controlled trial (RCT) is to assess the effectiveness of a multimodal manual therapy treatment compared to usual care for the prophylactic treatment of migraine.

Methods

This study is a single blinded, multicentre, pragmatic clinical trial, with two parallel groups assessing the potential superiority of a multimodal MT treatment over usual care by the GP. We will include a four weeks run-in period to provide accurate migraine frequency data prior to enrolment. The treatment will last 12 weeks with follow-up measurements at 12, 26 and 52 weeks (Figure 1). The study adheres to the guidelines of the International Headache Society (IHS) for controlled trials in patients with migraine regarding inclusion criteria, outcome measurements and statistical analysis [9].

Parallel to the RCT we will conduct a prospective cohort study with migraine patients with a strong preference for MT treatment who do not want to be randomized. The aim of this parallel group is to explore the differences in patient characteristics at baseline between the randomized trial and the cohort study. Patient's expectations with regard to recovery will be assessed in both studies and the relationship between expectations and effect of the treatment, i.e. the primary outcome measures, will be analysed. This information is necessary to better understand the generalizability of the study results. The participants in the cohort study will be treated with MT; treatment and measurements will be identical to the treatment procedure and measurements used in the RCT. All measurements will take place by a trained research assistant at one location. Participants will be given usual care by their own GP.

The design and protocol of the study have been approved by the medical ethics committee of Amsterdam University Medical Centers (location VUmc) and registered in the Dutch Trial Register (NL7504) The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) for this research is available in Additional file 1 [28].

Population

Participants will be recruited by the participating general practitioners (GPs) working in an urban area of Hoofddorp, The Netherlands. During consultation, the GP will provide oral and written information about the study and will invite the patient to participate. If the patient is interested in participating in the study and consents in providing contact details to the researcher, the GP notifies the researcher by email. The researcher will provide additional information about the study to the participant, followed by a telephone interview after one week to answer possible questions and check inclusion and exclusion criteria.

Inclusion criteria

Eligible participants are between 18–65 years of age and should have had migraine attacks for more than one year, according to the diagnostic criteria of the International Classification of Headache Disorders (ICHD) III [29]. A GP or neurologist should have established the diagnosis migraine, and the frequency of attacks should be two times a month or more. Co-occurrence of tension-type headache is allowed if the participant can clearly distinguish this headache from migraine. Participants will only be included if they have concomitant neck pain between migraine attacks or during an attack. The use of prophylactic medication is allowed if migraine is stable and medication use has not changed in the last three months. Furthermore, participants have to be able to read and write Dutch.

Exclusion criteria are (suspected) malignancy, pregnancy, cerebrovascular disease, degenerative central nervous system diseases, medication-overuse headache, a current diagnosis of depression or other severe psychiatric disease, rheumatoid arthritis, serious or systemic infection, fever, or change in medication for migraine within three months before the study, and having received MT treatment for migraine up to three months prior to the start of the study.

Data collection

Participants are asked to keep a headache diary, in order to obtain baseline data for migraine characteristics, and will receive an appointment with the research assistant after four weeks. Before baseline measurement, the research assistant will check inclusion and exclusion criteria and ask for written informed consent. Four weeks before the follow-up appointment, participants will be asked by email or telephone to start filling out a headache diary.

Figure 1.

Fig. 1 Flow diagram of the trial

Baseline assessment

Baseline assessment will include the registration of demographic variables (age, gender, education and profession), migraine characteristics according to ICHD III criteria, other physical complaints and chronic diseases.

Expectations regarding the effectiveness of treatment will be measured on a 7-point rating scale (range from no result (0), to excellent result expected (6)). Patient's preference for treatment will be administrated (preference for usual care, MT or no preference). Other outcome measures include disability (Headache Impact Test questionnaire (HIT–6)) [30], allodynia (allodynia questionnaire) [31], pressure pain thresholds [32] and neck flexor muscle endurance [33] (see below for details). *Figure 2.* shows all outcome measures and assessments.

Figure 2.

Fig. 2 Schedule of outcome measures and assessments

Randomization

After baseline measurement, randomization will take place with a 1:1 allocation ratio. An independent statistician who has no involvement with the clinical investigators will generate a random sequence of numbers before the start of the study. The research assistant who is blinded for the randomization sequence will supply sealed and numbered envelopes. In the presence of another administrative assistant, the participant will open the sealed envelope, and an appointment will be made for treatment by either the participating GP or a manual therapist. Participants will be invited to a parallel cohort study if a strong preference for MT treatment keeps them from agreeing with randomization.

Blinding

Allocation of participants is concealed from the researcher and the research assistant who performs all measurements. An independent statistician will carry out the statistical analysis and review the interpretation of the results. For obvious reasons, participating patients, GPs and manual therapists cannot be blinded to treatment.

Usual care

Participants assigned to the usual care group will be treated by their GP. The GP will treat participants as usual, based on the recommendations of the practice guideline for headache of the Dutch College of General Practitioners [34]. The general practitioner (GP) provides lifestyle advice and, if necessary, prescribes medication. The recommended treatment consists of acute medication for a single attack or prophylactic medication when the migraine attacks occur two times a month or more [5]. The GP will evaluate the treatment in consecutive appointments. Participating GPs will be informed about the research protocol by the researcher during a one-hour meeting.

Intervention

The multimodal manual therapy treatment aims at restoring cervical function in order to reduce nociceptive cervical afferent output. The treatment will include manual pressure techniques on the trapezius muscle and upper cervical/suboccipital musculature to decrease neck pain intensity and cervical muscle tenderness [35]. Neck muscle strength will be trained, by giving low load craniocervical muscle exercises and correcting sitting and standing posture [36]. The selected spinal mobilizations are low and high-velocity techniques of the cervical and thoracic spine. No high-velocity techniques will be applied to the upper cervical region (C0–3) because of the risk of serious adverse events [37].

Experienced manual therapists will be trained in the treatment protocol prior to the study. The treatment protocol provides recommendations of techniques that can be used; the treating manual therapist decides which techniques will be included, depending on the condition of the participant. The applied techniques will be documented for each session on an evaluation form. Instructions on posture and home exercises will be provided to the participants in booklets. The MT intervention will consist of a maximum of 9 sessions of 30 minutes starting with treatment once a week, followed by once every other week during 12 weeks.

During the 12 weeks of treatment, participants will be asked not to make use of additional therapies or medication for their migraine. At all follow-up measurements possible use of additional therapies and medication will be asked for and registered.

Primary outcome measure

The primary outcome of the study is the number of migraine days, recorded by the participant in a headache diary during all follow-up assessments. [9]. A migraine day is defined as a day with migraine characteristics according to the IHS classification ICDH III for longer than four hours, or a headache that resolves with the intake of triptans or ergotamine within two hours of intake [29].

Secondary outcome measures

The secondary outcome measures are:

1. Number of migraine attacks per four weeks, recorded in a headache diary during the four weeks before follow-up measurements [9]. Migraine attacks will be considered as separate attacks if a full day without headache is reported in the headache diary between migraine days.
2. Pain intensity of migraine, assessed on an 11 point numerical rating scale (0 = no pain, 10 = most severe pain) [38].
3. Medication use in number of doses per 4 weeks of simple analgesics (e.g., paracetamol), NSAIDs, acute migraine medication (triptans and ergotamines) or prophylactic medication. Participants are asked to report changes of medication to the research assistant at all follow-up measurements.
4. Responder rate will be measured by the number of migraine days before vs. after treatment, dichotomized into ≥50% reduction or not [9].
5. Disability, assessed by the HIT–6 questionnaire. The HIT–6 consists of 6 questions measuring pain intensity, social functioning, role functioning, vitality, cognitive functioning and psychological distress on a 5-point ordinal rating scale (never to always). Internal consistency is considered high (Cronbach's alpha 0.82 to 0.90), and test-retest reliability is fair (ICC 0.77) [30]. The Dutch version of the HIT–6 questionnaire has shown to be a valid and reliable tool to measure the impact of migraine [39].
6. The endurance of the neck flexor muscles will be scored as the number of seconds the participant can raise his head from the table when lying in supine position as described by Harris et al. (2005). Harris et al. reported good to excellent intra-tester reliability (ICC 0.82–0.91) and moderate inter-tester reliability (ICC 0.67–0.78) [33].
7. Cutaneous allodynia (CA) will be evaluated with the 12-item allodynia symptom checklist. This questionnaire consists of 12 questions about cutaneous hypersensitivity in the cervical cephalic region. The participant can score yes, no, or not applicable. Allodynia symptoms and score on CA severity are defined in the following categories: none (0–2), mild (3–5), moderate (6–8) and severe (9 or higher) [31].
8. We will perform algometry, by measuring pressure pain thresholds (PPT) with a Wagner FDK algometer at the upper trapezius muscle (at the midpoint between C7 spinosus and the acromion), the suboccipital muscles and the anterior tibial muscle. The PPT measurement will be repeated three times at each point, and a mean score will be calculated. Algometry has demonstrated excellent intra-tester reliability (upper trapezius test-retest ICC 0.83, 95% CI 0.69–0.91), and excellent inter-tester reliability (upper trapezius ICC 0.89, 95% CI 0.83–0.93) [32].
9. Participants will be asked to report global perceived effect on a 7 point rating scale (0 = much worse to 6 = much better). Disability due to attacks will be assessed on a 5 point rating scale (0 = no disability and no medication to 4 = fully disabled even with medication). Also, use of healthcare resources and absence of work will be reported.
10. All adverse events will be administrated for both treatments at all follow-up measurements.

Statistical analysis

Baseline characteristics will be presented in percentages for categorical variables, and in means and standard deviations for continuous data, using descriptive statistics. The distribution of the data will be evaluated using histograms and QQ-plots. The outcomes will be adjusted for baseline differences. The outcomes of the total follow-up period, including baseline data, will be examined with a linear mixed model analysis. Differences between groups will be reported and shown in tables. Differences between the cohort group and the RCT groups (separate and combined) will be analyzed with Student T-tests (continuous data) and Chi-squared tests (nominal data). For non-parametric data, the Mann-Whitney U test will be used. The primary analysis will be by intention-to-treat. Additionally, a per-protocol analysis will be carried out to assess the effect in participants who adhered to the protocol. Protocol adherence will be defined as staying in the allocated treatment group during the 12-week treatment period; for MT treatment, participants have to complete at least six sessions. In the 'usual care' group, participants who receive MT during the 12-week period will be excluded from the per-protocol analysis. Effect sizes will be computed for normally distributed outcomes. Statistical analysis will be carried out using SPSS version 23 (IBM Corporation, Armonk, NY).

Sample size

Taking pilot study results as the basis for our calculation, we assume an average frequency of migraine days in the 4 weeks before the 26th week measurement point of 4.2 days (SD 2.4). As we want to detect a difference in the reduction of the number of migraine days of at least 25% between groups, with a two-sided significance level of 0.05 and a power of 0.80, each group will have to include 83 evaluable persons. Taking into account a 15% loss to follow-up, a total of (100/85)*83*2 = 196 participants will have to be enrolled into the study, 98 per group.

To ensure the enrolment of the required number of participants over an estimated period of two years, we will recruit 44 GPs and four manual therapists to participate in the full trial.

Feasibility of the study

We performed a pilot study to assess the feasibility of the measurements, the treatment protocol and randomization procedures. The pilot study concerned 24 possible participants in eight weeks (October 2015 to December 2015); 11 participants fulfilled the inclusion criteria.

Two out of 13 excluded participants had a strong preference for manual therapy treatment and, therefore, were excluded from randomization. Other reasons for exclusion were: no migraine according to the IHS criteria, low frequency of migraine and participants with GPs who did not participate in the pilot study. The research protocol was evaluated by questionnaires and in personal meetings with the participating manual therapists, GPs, research assistant and participants. GPs and MT reported no problems with adhering to the protocol for measurements and treatment. The results of the pilot study showed that the treatment protocol and procedures were feasible and that the participants tolerated both treatments well.

Discussion

We have described the design of an RCT to assess the effectiveness of a multimodal MT intervention for the treatment of migraine. We performed a pilot study to evaluate the feasibility of our protocol and procedures. The results of this pilot were encouraging; the expected recruitment was accomplished within a period of eight weeks, participants tolerated the MT treatment protocol and measurements without problems.

MT is a commonly used non-pharmacological treatment for migraine in primary care [12]; however, the evidence of MT to reduce migraine attacks is scarce and shows methodological flaws. Therefore, with this trial, we attempt to strengthen the evidence and to minimize the methodological shortcomings.

A strength of our design is that we adhere to the clinical trial guideline of the IHS concerning the inclusion and exclusion criteria for migraine and statistical analysis. This will make it is possible to provide a more robust conclusion on the effectiveness of the MT.

Although the IHS guidelines recommend both the number of migraine days and the number of migraine attacks as the primary outcome, we have included only one primary outcome: the number of migraine days. To report one primary outcome is in line with the CONSORT statement [40]. Furthermore, we believe that the number of migraine days is a relevant clinical outcome and will be more responsive to change.

A strength of this study is that we compare state-of-the art, guideline-based usual care with a new treatment option. Moreover, a pragmatic trial with two regularly applied treatments will enhance external validity of the results [41] and is in line with other studies [36][42].

Our study has a few limitations. One of the limitations concerns the absence of blinding of participants, manual therapists and GP's. Furthermore, the participant will receive information about the treatment and the intended goal, which may lead to information bias.

We did not include a placebo or sham manual therapy treatment as a control intervention, but chose to compare two active and commonly used treatment interventions in a primary care setting. We argue that it would be unethical to withhold an effective prophylactic treatment as a comparator for patients with frequent migraine.

In this study, we will use the 12-item allodynia symptom checklist to evaluate cutaneous allodynia. This checklist is validated using quantitative sensory testing as a gold standard, but needs further validation for reliability and responsiveness [31].

The pilot study showed that 15% of the participants had a preference for the MT treatment, which withheld participants from being randomized. Separate from the RCT, a parallel cohort study will be conducted for this group to compare these results with the RCT outcomes. Expectations regarding treatment outcome will be assessed in both the RCT and the cohort study because these could influence differences in outcomes.

The results of this study will be published in peer-reviewed journals in agreement with the CONSORT 2010 statement [40]. This study aims to produce evidence pertaining to non-pharmacological prophylactic treatments for migraine. The results of this study may support patients and GPs in their decision making in search for prophylactic treatment options to reduce the burden that migraine has on personal life and society.

Trial status: Protocol version 5, date: 13–06–2019. The study is in the recruitment phase. Recruitment period is estimated from April 8th 2019 to May 2021.

Abbreviations

MT: manual therapy; GP: general practitioner; IHS: International Headache Society; RCT: randomized controlled trial; ICHD: International Classification of Headache Disorders; VUmc: VU university Medical Centre; CA: cutaneous allodynia; PPT: pressure pain thresholds.

Declarations

Ethics approval:

The study “Manual therapy as a prophylactic treatment for migraine. A randomized controlled trial” is approved by the ethics committee of Amsterdam University Medical Centers (location VUmc),(registration number 2018.387). For this study central ethical approval has been confirmed from the ethics committee of Amsterdam University Medical Centers (ref approval no. 2018.387) and we will not begin recruiting at other centres in the trial until local ethical approval has been obtained.

Informed consent will be obtained from all study participants in this study.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets of the study will be available from the corresponding author on reasonable request.

Funding:

The Healthcare Centre Haarlemmermeer (www.gchaarlemmermeer.nl) will fund local facilities and time for the researcher and research assistant. The funder was not involved in the design of the study and will

not be involved in data collection.

Competing interests:

The authors declare to have no competing interests.

Contributors:

AA drafted the manuscript. RC and AA had the original idea for the study. RC, JCvdW, WdH, JD and HvdH all provided critical revisions and contributions to the study design. All authors read and approved the final manuscript.

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Figures

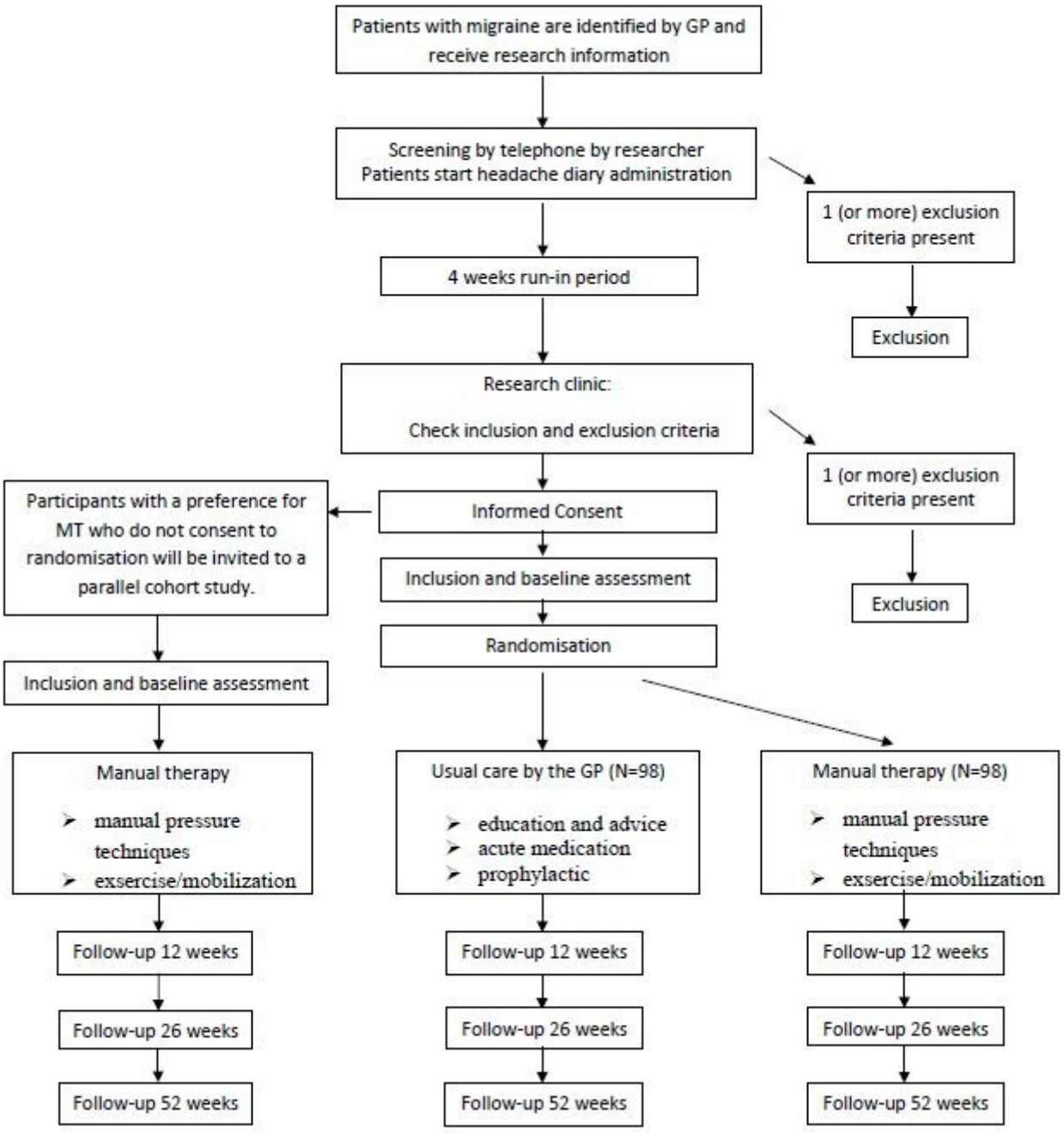

Figure 1

Flow diagram of the trial

Outcome	Measurement	Base-line	12 weeks	26 weeks	52 weeks
Primary outcome measures					
Migraine days	Headache diary	X	X	X	X
Secondary outcome measures					
1. Migraine attacks	Headache diary	X	X	X	X
2. Migraine intensity	Numeric Rating Scale	X	X	X	X
3. Medication use	Headache diary	X	X	X	X
4. 50% migraine days reduction rate	Headache diary		X	X	X
5. Disability in daily life	Hit-6 questionnaire	X	X	X	X
6. Endurance of the neck flexor muscles	Muscle endurance test	X	X	X	X
7. Allodynia	Allodynia questionnaire	X	X	X	X
8. Algometry (pressure pain thresholds)	Wagner Algometer	X	X	X	X
9. Global perceived effect	7 point rating scale		X	X	X
Experienced disability of attacks	7 point rating scale		X	X	X
Absence of work related to migraine	Headache diary		X	X	X
Use of health care during the trial	Headache diary		X	X	X
10. Adverse events	Administration follow-up		X	X	X

Figure 2

Schedule of outcome measures and assessments

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplement1.doc