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Protocol

The effectiveness of acupuncture and mindfulness-based stress reduction (MBSR) for patients with multiple sclerosis associated fatigue – A study protocol and its rationale for a randomized controlled trial

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ABSTRACT

Introduction: Fatigue plays an important role in the daily activity of patients with multiple sclerosis (MS) and strongly influences their quality of life. Numerous clinical trials evaluating various interventions for fatigue in MS have shown only minor benefits. The main aim of the present trial is to evaluate whether 1) acupuncture or 2) mindfulness-based stress reduction (MBSR) in addition to usual care are effective in reducing fatigue in MS patients compared to usual care alone.

Methods: Within a randomized, three-arm, controlled trial we aim to include 141 MS patients aged 18–65 years with fatigue for at least 3 months and an average score of ≥ 4 on the Fatigue Severity Scale (FSS). Patients will be randomized into three groups: an acupuncture group receiving 12 weeks of acupuncture in addition to usual care, a MBSR group receiving 12 weeks of MBSR in addition to usual care, and a usual care group continuing their previous treatment. Primary outcome is the Fatigue Severity Scale (FSS) after 12 weeks. To assess the trial's characteristics regarding efficacy and effectiveness we used the pragmatic explanatory continuum summary (PRECIS-2).

Discussion: This trial addresses new therapeutic approaches for fatigue in MS. The resulting design is a compromise between scientific rigor and pragmatism. Due to difficulties with recruitment we had to scale down our trial to the groups of usual care and acupuncture. The trial's results will give first evidence whether acupuncture is effective in patients with MS associated fatigue.

Trial registration: ClinicalTrials.gov identifier NCT01864707, registered on 2 April 2013.

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1. Background

Multiple sclerosis (MS) is a chronic, unpredictable, incurable, demyelinating disease of the central nervous system affecting approximately 2.5 million people worldwide [1,2]. Fatigue is the most common clinical symptom, reported by up to 97% of MS patients [3–7]. The MS-related fatigue is defined as a subjective lack of physical or mental energy or both that is perceived by the individual or caregiver to interfere with usual or desired activities [8,9]. It has to be differentiated from fatigue secondary to depression, cognitive dysfunction, poor sleep, or motor impairment. It may be the first presenting system of MS and even the only manifestation of an acute relapse. Fatigue has a substantial negative impact on quality of life, and is a major cause of unemployment for MS patients [10–12]. However, the pathophysiology of fatigue is still not completely understood and the treatment of fatigue remains difficult [7]. A number of clinical trials for fatigue in MS have shown some minor benefits for different interventions, including medication, physical activity, cognitive-behavioral therapy and deep transcranial magnetic stimulation [13–19]. Many MS patients are dissatisfied with medical management due to perceptions that the medication has a range of unpleasant side effects, which leverages the use of alternative therapies [20].

Mindfulness-based stress reduction (MBSR) has been increasingly applied in neuropsychological rehabilitation of MS patients to reduce anxiety levels and to improve psychological well-being in stressful situations [21]. A review comprising the few controlled studies published of MBSR in MS concludes that MBSR may be of benefit regarding quality of life, anxiety and depression as well as fatigue. More high quality studies are needed to investigate feasibility, practicality, acceptability, health and psychosocial benefits of MBSR for people with MS [22].

Acupuncture has been frequently mentioned as a non-pharmacological means of managing the disease, with a prevalence of its usage reported from 7.2% to 21% of the MS population [23,24]. However, although many of the studies in a review from 2014 suggested that acupuncture was successful in improving MS related symptoms, lack of statistical rigor and poor study design make it difficult to draw any conclusions about the true effectiveness of this intervention in the MS population [25]. Further research and the development of more targeted therapies are needed to improve the management of fatigue [13]. Our study aims to evaluate the effectiveness of acupuncture and mindfulness-based stress reduction (MBSR) for patients with MS associated fatigue.

Here, we describe the study protocol of this comprehensive translational trial run by a multidisciplinary group. The trial addresses these new therapeutic approaches for fatigue in MS and applies experimental and clinical methodology. In addition, we report the trial's characteristics regarding efficacy and effectiveness using the pragmatic explanatory continuum summary (PRECIS-2) and explain the rationale and obstacles of the trial design.

2. Methods/design

2.1. Study design

This study is a randomized, 3-arm controlled trial (Fig. 1) performed at the Charité – Universitätsmedizin Berlin including three arms in a 1:1:1 fashion: 1) a usual care group continuing their previous treatments, 2) an acupuncture group receiving 12 weeks of standardized acupuncture treatment in addition to usual care, and 3) an MBSR group receiving 8 weeks of MBSR training plus an additional workshop within 12 weeks in addition to usual care. The primary outcome is recorded after 12 weeks; follow-up measurements are performed after 26 weeks. Recruitment started in April 2013. This manuscript is based on the study protocol version 1.1 of September 2013.

2.2. Ethical considerations

The study was approved by the ethics committee of the Charité – Universitätsmedizin Berlin (Application number EA1/026/12). This study follows the standards of the Declaration of Helsinki [26], and the ICH-GCP guideline. The study has been reviewed and approved by the data protection officer of the Charité – Universitätsmedizin Berlin. The potential benefits and risks of the study are fully explained to the patients. All patients provide written informed consent before participating in the study. The study was registered before inclusion of the first patients at clinicaltrials.gov (Number NCT01864707).

2.3. Participants

Patients are recruited by one study center with wide experience in research projects on MS (NeuroCure Clinical Research Center, Charité – Universitätsmedizin Berlin, Berlin, Germany). Patients from the existing patient pool are asked for participation, and patients outside the university setting are recruited by using information material including brochures, handouts, and articles in magazines focussing on MS patients. Participating in the study is free of charge, no compensation is paid.

We include female and male patients aged 18–65 years with the clinical diagnosis of MS [27] and fatigue for at least 3 months, and a fatigue score ≥ 4 on the Fatigue Severity Scale (FSS, [28]) at inclusion. Additional inclusion criteria are that other pre-study treatments with respect to target symptom fatigue have been unchanged for at least 3 months before inclusion, the immunomodulatory or immunosuppressive therapy regime has been unchanged for at least 3 months before inclusion. Patients have to be mentally and physically able to participate in the trial. They have to be willing to be randomized, to attend visits, to complete questionnaires, and to participate in fMRI measurements.

Patients are not eligible if they fulfil at least one of the following exclusion criteria: fatigue caused by a malignant disease, acute relapse or corticosteroid therapy in the last 30 days before inclusion, Extended Disability Status Scale (EDSS, [29]) > 6.0, Beck Depression Inventory, second edition (BDI-II, [30]) > 28, fatigue specific acupuncture during the previous 12 months before inclusion, practice of formerly learned MBSR exercises during the previous 12 months, change of immunomodulatory or immunosuppressive therapy during the 3 months before inclusion, other new therapies planned which could have a positive effect on fatigue (e.g. exercise, relaxation therapy), pregnancy or anticipated pregnancy during the intervention period, severe acute and or chronic disease which do not allow participation in the study, other limitations which do not allow participation in the therapy (e.g. bleeding disorder). Additional exclusion criteria include contraindications for fMRI sessions (e.g. metal clips), alcohol or substance abuse, and parallel participation in another interventional clinical trial.

During the initial phase of the trial (April 2013 and August 2013) after the recruitment of 18 patients inclusion and exclusion criteria were adapted: Because numerous patients older than 60 were interested to participate in the study the maximum patient age was changed from 60 to 65 years. Moreover, patients with an FSS score ≥ 4 points (instead of ≥ 5) were included to allow the participation of patients with less severe fatigue. In consideration that there is a wide clinical overlap of symptoms of fatigue and depression we extended the exclusion criterion BDI from a score of > 19 to a score of > 28. The experience with the first study participants revealed that walking ability was not a mandatory requirement for actively attending MBSR, therefore patients with an EDSS score of > 6.0 points instead of > 5.0 could be included. Because of recruitment problems, in July 2014 we decided to stop recruitment for the MBSR group after the allocation of 21 patients to that group. We stopped recruitment for MBSR and not for acupuncture because patients eligible for the study were more interested in receiving acupuncture than in MBSR. Recruitment continued only for the usual care and the acupuncture group until March 2015.