Meditation for adult patients with haematological malignancies (Protocol)

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[Intervention Protocol]

Meditation for adult patients with haematological malignancies

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

This review aims to detect benefits and harms of meditation practice as an additional treatment to standard care for adult people with haematological malignancies.

BACKGROUND

Description of the condition

Haematological malignancies are neoplasms of the blood, lymph nodes and bone marrow. They can either derive from myeloid or lymphoid blood cell lines. Malignant neoplasms concerning the myeloid cells are acute and chronic myelogenous leukaemia, myelodysplastic syndrome or myeloproliferative diseases whereas lymphocytic leukemias, myelomas and lymphomas are of lymphoid origin. In 2010, the prevalence of people living with leukaemia in the United States adds up to approximately 287,963 men and women. The age-adjusted incidence rates for haematological cancer patients per 100.000 men and women per year came up to 22.5% for lymphoma, 12.8% for leukaemia and 5.9% for patients suffering from myeloma. The overall five year survival rate for lymphoma patients is 71%, whereas leukaemia has a survival rate of 56% and only 43.2% of myeloma patients live for more than five years after being diagnosed with cancer (Howlader 2013).

The number of different treatment options available for haematological malignancies is probably just as high as the differences between the individual survival rates. Depending on the severity of symptoms and disease progression rate, some people may only need supportive care to reduce the symptoms that occur alongside their disease such as anaemic symptoms, osteoporosis or infections. There is a wide range of specific blood cancer therapy treatments like chemotherapy, combined drug therapy, radiation and stem cell transplantation (Longo 2011).

Description of the intervention

Meditation has its origins in ancient eastern traditions and is seen as a mind-body practice in complementary and alternative medicine (NCCAM 2013). Meditation practice has derived from a group of techniques, like mindfulness meditation,

mantra meditation, relaxation response and Zen Buddhist meditation.Throughout thousands of years, these techniques have been practised by many different cultures. For practising meditation you most commonly have to consider several circumstances, such as finding a quiet location and a fitting posture. Meditation can be practised while sitting, standing or lying down. You can either concentrate on your own breath, objects, or on a mantra, which can be a chosen word, or a pair of words. It is also important to have an open attitude, which means you have to let distractions come and go, so that they can not affect your thoughts (NCCAM 2013).

Mindfulness-based cognitive therapy has shown improvement on distress, depression and anxiety, as well as quality of life in patients diagnosed with cancer (Foley 2010). Another study using mantra based meditation has shown an improvement in perceived stress and negative mood and also pointed out, that the frequency of the use of meditation could affect the outcomes (Lane 2007). Spiritually focused meditation is another way to consider the religious and spiritual needs of leukaemia patients (Cole 2010).

Mindfulness is the source of several clinical practices and can be used in mental training or by performing different types of meditation (Carlson 2005). Mindfulness-based stress reduction, as a clinical intervention using mindfulness as its fundament has shown several significant positive effects for a heterogeneous group of 63 cancer patients in terms of mood and sleep disturbance, stress and fatigue (Carlson 2005). Mindfulness-based stress reduction is a textured group programme, designed to lighten symptoms of patients suffering from psychosomatic or physical disorders, using mindfulness meditation (Grossman 2004). Cancer patients often suffer from sleep disturbances, which are difficult to treat, because the causes of these disturbances can not always be detected (Carlson 2005). Spiritual and religious conceptions of cancer patients should also be respected in cancer care and may, when integrated into meditations, enhance the effects of mediation practice (Cole 2010).

How the intervention might work

The exact mechanism of how meditation can improve ones mood and has positive effects on the cognition of stress is not determined, but evidence in studies with healthy adults showed, that even short instructions in meditation techniques can lead to health benefits that last for a long time (Lane 2007). Although derived from a relatively small number of studies, these results suggest that mindfulness-based stress reduction may help a broad range of individuals to cope with their clinical and non-clinical problems (Grossman 2004).

Preliminary evidence suggests that even a brief instruction in a simple meditation technique can improve negative mood and perceived stress in healthy adults, which could yield long-term health benefits. Frequency of practice does affect outcome. Those most likely to experience negative emotions may benefit the most from the intervention (Lane 2007).

One randomised controlled trial (RCT) in more than 100 patients showed that meditation can not only have an effect on a person's mental state, but also on his physiological mechanisms of regulation by affecting the regulation of the blood pressure (Carlson 2007; Schneider 1995; Schneider 2006).

Why it is important to do this review

Little is known about the prevalence of mood disorders such as anxiety or depression in haematological patients. There is one meta-analysis of 70 interview-based studies concerning patients in oncological and haematological settings, that indicated a prevalence rate of 20.7% for depression (Mitchell 2011).

Variable studies have shown positive outcomes on stress, fatigue and sleep quality for either healthy, physically or psychologically diseased people by performing various meditation techniques and using mindfulness practices (Grossman 2004; Kang 2012; Lane 2007; Witek-Janusek 2008).

There are several existing RCTs which have shown positive effects of mindfulness-based stress reduction for breast cancer patients (Carlson 2005: Cramer 2012; Foley 2010; Witek-Janusek 2008). Some evidence has been shown in enhancing the psychological health of breast cancer patients (Cramer 2012). Even cortisol levels have been reduced in patients following the mindfulness- based stress reduction programme. Benificial effects on immune function and the quality of life, as well as for coping processes of breast cancer patients were discovered (Witek-Janusek 2008). Although those studies were not specifically designed for patients suffering from haematological malignancies, it may be assumed that meditation and mindfulness-based stress reduction might also be advantageous for haematologically diseased patients.

OBJECTIVES

This review aims to detect benefits and harms of meditation practice as an additional treatment to standard care for adult people with haematological malignancies.

METHODS

Criteria for considering studies for this review

Types of studies

We will only consider RCTs. We will include both full text and abstract publications if sufficient information is available on study design, characteristics of participants, interventions and outcomes. The trials had to report at least one of the outcomes mentioned below to be included.

Types of participants

We will include trials on adult (≥ 18 years) patients with confirmed diagnosis of haematological malignancies. We will not apply gender or ethnicity restrictions. We will consider all subtypes and stages of haematological malignancies, including newly diagnosed patients and those with relapsed or drug resistant disease. If trials consist of mixed populations with different conditions or type of cancers, we will use data from the haematological malignancy subgroups. If subgroup data for these patients is not provided (after contacting the authors of the trial), we will exclude the trial if less than 80% of patients have haematological malignancies.

Types of interventions

The intervention will be meditation in addition to standard care compared with standard care only. We will include any form of meditation.

Types of outcome measures

Primary outcomes

We will evaluate quality of life as the primary efficacy endpoint. It should be measured with reliable and validated instruments.

Secondary outcomes

We will analyse the following outcomes as secondary outcomes.

- Overall survival, defined as the time interval from random treatment assignment onto a study to death from any cause or to the last follow-up.
- Fatigue if measured with reliable and validated instruments.
- Anxiety if measured with reliable and validated instruments.
- Depression if measured with reliable and validated instruments.
- Quality of sleep if measured with reliable and validated instruments.
- Adverse events.

Search methods for identification of studies

Electronic searches

We will adapt the search strategies suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We will apply no language restriction to reduce the language bias. We will search the following databases and sources.

- Databases of medical literature:
  - the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, latest issue) (Appendix 1);
  - MEDLINE (Ovid) (1950 to present) (Appendix 2).
- Databases of ongoing trials:
  - the *meta*Register of Controlled Trials (*m*RCT) (http://www.controlled-trials.com/mrct/).
- Conference proceedings of annual meetings of the following societies for abstracts, if not included in CENTRAL (2010 to present):
  - American Society of Hematology;
  - American Society of Clinical Oncology;
  - European Hematology Association;
  - European Congress for Integrative Medicine;
  - Global Advances in Health and Medicine (2011 to 2014).

Searching other resources

- Handsearching of references
  - References of all identified trials, relevant review articles and current treatment guidelines for further literature

Data collection and analysis

Selection of studies

Two review authors will independently screen the results of the search strategies for eligibility for this review by reading the abstracts. In the case of disagreement the full text publication will be obtained. If no consensus can be reached, we will ask a third review author (Higgins 2011a).

We will document in a flow chart as recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher 2009), showing the total numbers of retrieved references and the numbers of included and excluded studies.

Data extraction and management

Two review authors will independently extract the data according to the guidelines proposed by The Cochrane Collaboration (Higgins 2011a). We will contact authors of individual studies for additional information, if required. We will use a standardised data extraction form containing the following items.

- General information:

- author, title, source, publication date, country, language, duplicate publications.
- Quality assessment:
  - allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias.
- Study characteristics:
  - trial design, aims, setting and dates, source of participants, inclusion/exclusion criteria, comparability of groups, subgroup analysis, statistical methods, power calculations, treatment cross-overs, compliance with assigned treatment, length of follow-up, time point of randomisation.
- Participant characteristics:
  - underlying disease, stage of disease, histological subtype, additional diagnoses, age, gender, ethnicity, number of participants recruited/allocated/evaluated, participants lost to follow-up, type of treatment (multi-agent chemotherapy (intensity of regimen, number of cycles)), additional radiotherapy.
- Interventions:
  - type, duration and intensity of meditation intervention, standard care, duration of follow-up.
- Outcomes:
  - overall survival, quality of life, fatigue, anxiety, depression, quality of sleep, adverse events.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias for each study using the following criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b):

- sequence generation;
- allocation concealment;
- blinding (participants, personnel, outcome assessors);
- incomplete outcome data;
- selective outcome reporting;
- other sources of bias.

We will make a judgement for every criterion, using one of the following three categories.

1. 'Low risk': if the criterion is adequately fulfilled in the study, i.e. the study is at a low risk of bias for the given criterion.
2. 'High risk': if the criterion is not fulfilled in the study, i.e. the study is at high risk of bias for the given criterion.
3. 'Unclear': if the study report does not provide sufficient information to allow for a clear judgement or if the risk of bias is unknown for one of the criteria listed above.

Measures of treatment effect

We will use intention-to-treat data. For binary outcomes, we will calculate risk ratios (RRs) with 95% confidence intervals (CIs) for each trial. For time-to-event outcomes, we will extract hazard ratios (HRs) from published data according to Parmar 1998 and Tierney 2007. We will calculate continuous outcomes as standardised mean differences (SMDs).

Dealing with missing data

As suggested in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c), there are many potential sources of missing data which have to be taken into account: at study level, at outcome level, and at summary data level. Firstly, it is important to distinguish between 'missing at random' and 'not missing at random'. We will contact the original investigators to request missing data. If data are still missing, we will make explicit assumptions of any methods used; for example, that the data are assumed to be missing at random or that missing values are assumed to have a particular value, such as a poor outcome. We will impute missing data for patients who were lost to follow-up after randomisation (dichotomous data) assuming poor outcome (worse case scenario) for missing individuals. We will perform sensitivity analysis to assess how sensitive results are to reasonable changes in the assumptions that are made. We will address the potential impact of missing data on the finding of the review in the discussion.

Assessment of heterogeneity

We will assess heterogeneity of treatment effects between trials using the Chi^2 test with a significance level at $P < 0.1$. We will use the I^2 statistic to quantify possible heterogeneity ($I^2 > 30\%$ moderate heterogeneity, $I^2 > 75\%$ considerable heterogeneity) (Deeks 2011). We will explore potential causes of heterogeneity by sensitivity and subgroup analysis.

Assessment of reporting biases

In meta-analyses with at least 10 trials, we will investigate potential publication bias by generating a funnel plot and statistically tested by using a linear regression test (Sterne 2011). A P value of less than 0.1 will be considered significant for this test.

Data synthesis

Should the data be considered sufficiently similar to be combined, we will pool the results by applying meta-analyses using the random-effects model, while we will use the fixed-effect model as a sensitivity analysis. If the trials are clinically too heterogenous to combine (e.g. various types of diseases), we will perform subgroup analyses only without calculating an overall estimate. If different tools are used to evaluate quality of life, fatigue, anxiety, depression or quality of sleep, we will calculate the SMDs to perform a meta-analysis. We will perform analyses according to the recommendations of The Cochrane Collaboration (Deeks 2011), and will use The Cochrane Collaboration's statistical software, Review

Manager 2014, for analysis. We will create a 'Summary of findings' table on absolute risks in each group according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (GRADEpro 2008; Schünemann 2011). We will summarise the evidence of overall survival, quality of life, fatigue, anxiety, depression, quality of sleep and adverse effects in this 'Summary of findings' table.

Subgroup analysis and investigation of heterogeneity

We will consider performing subgroups using the following characteristics:

- entity (indolent non-Hodgkin lymphoma, aggressive non-Hodgkin lymphoma, acute leukaemia, chronic myeloid leukaemia, multiple myeloma, chronic lymphocytic leukaemia, Hodgkin lymphoma) of underlying disease;
- antic-cancer therapy (first-line therapy, relapse therapy);
- type/duration/intensity of meditation.

Sensitivity analysis

We will perform the following sensitivity analyses:

- quality components with regard to low and high risk of bias;
- fixed-effect modelling.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

1	MeSH descriptor: [Mind-Body Therapies] explode all trees
2	body-mind*
3	mind-body*
4	(mind-body near/3 (program* or therap* or medicin*))
5	#1 or #2 or #3 or #4
6	mindfulness based stress reduction*
7	mindfulness based*
8	mbsr* or mbct*
9	MeSH descriptor: [Meditation] explode all trees
10	meditation*
11	MeSH descriptor: [Relaxation Therapy] explode all trees
12	(relaxation* near/2 (technique* or therap*))
13	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12
14	MeSH descriptor: [Hematologic Diseases] explode all trees
15	MeSH descriptor: [Hematologic Neoplasms] explode all trees
16	(hematolog* near/1 malignan*) OR (hematolog* near/1 neoplas*) OR (haematolog* near/1 malignan*) OR (haematolog* near/1 neoplas*)
17	MeSH descriptor: [Bone Marrow Diseases] explode all trees
18	MeSH descriptor: [Lymphoma] explode all trees
19	MeSH descriptor: [Leukemia] explode all trees
20	(hogkin* or hodkin* or hodgin*):ti,ab,kw
21	lymphogranulomato*
22	lymphom*

(*Continued*)

23	histiocy*
24	granulom*
25	non-hodgkin*
26	nonhodgkin*
27	Reticulosis
28	reticulosarcom*
29	(burkitt* NEAR/ (lymph* or tumo*))
30	brill-symmer*
31	plasm**ytom*
32	myelom*
33	Sezary
34	leuk*em*
35	myelodysplas*
36	aplast* an*em*
37	#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36
38	#13 and #37 in Trials

Appendix 2. MEDLINE search strategy

#	Searches
1	MIND-BODY THERAPIES/
2	body-mind$.tw,kf,ot.
3	mind-body$.tw,kf,ot.
4	(mind-body near/3 (program* or therap* or medicin*))

(*Continued*)

5	#1 or #2 or #3 or #4
6	mindfulness based stress reduction$.tw,kf,ot.
7	mindfulness based$.tw,kf,ot.
8	(mbsr$ or mbct$).tw,kf,ot.
9	MEDITATION/
10	meditation$.tw,kf,ot.
11	RELAXATION THERAPY/
12	(relaxation$ adj2 (technique$ or therap$)).tw,kf,ot.
13	or/6-12
14	5 or 13
15	HEMATOLOGIC DISEASES/
16	exp HEMATOLOGIC NEOPLASMS/
17	(hematolog$ adj1 malignan$).tw,kf,ot.
18	(hematolog$ adj1 neoplas$).tw,kf,ot.
19	(haematolog$ adj1 malignan$).tw,kf,ot.
20	(haematolog$ adj1 neoplas$).tw,kf,ot.
21	exp BONE MARROW DISEASES/
22	exp LYMPHOMA/
23	exp LEUKEMIA/
24	hodgkin$.tw,kf,ot.
25	lymphogranulomato$.tw,kf,ot.
26	lymphom$.tw,kf,ot.
27	histiocy$.tw,kf,ot.
28	granulom$.tw,kf,ot.

(*Continued*)

29	non-hodgkin$.tw,kf,ot.
30	nonhodgkin$.tw,kf,ot.
31	reticulosis.tw,kf,ot.
32	reticulosarcom$.tw,kf,ot.
33	(burkitt$ adj (lymph$ or tumo?r$)).tw,kf,ot.
34	lymphosarcom$.tw,kf,ot.
35	brill-symmer$.tw,kf,ot.
36	plasm##ytom$.tw,kf,ot.
37	myelom$.tw,kf,ot.
38	sezary.tw,kf,ot.
39	leuk?em$.tw,kf,ot.
40	myelodysplas$.tw,kf,ot.
41	aplast$ an?em$.ti,kf,ot.
42	or/15-41
43	randomized controlled trial.pt.
44	controlled clinical trial.pt.
45	randomi?ed.ab.
46	placebo.ab.
47	drug therapy.fs.
48	randomly.ab.
49	trial.ab.
50	groups.ab.
51	or/43-50
52	humans.sh.

(*Continued*)

53	51 and 52
54	14 and 42
55	54 and 53

CONTRIBUTIONS OF AUTHORS

Ines Salhofer (IS): conception and writing of the protocol.

Michaela Rancea (MR): advice and proof read.

Andrea Will (AW): advice and proof read.

Ina Monsef (IM): search strategy development.

Prof. Andreas Engert (AE): clinical expertise and advice.

Dr. Nicole Skoetz (NS): methodological and clinical expertise and advice, proof read.

All authors have read and accepted the final version of the review.

DECLARATIONS OF INTEREST

None known.

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