The PACT trial: PAtient Centered Telerehabilitation Effectiveness of software-supported and traditional mirror therapy in patients with phantom limb pain following lower limb amputation: design of a multicentre randomized controlled trial.

Human research ethics approval committee: Ethics committee of the Medical Faculty of Cologne University, Cologne, Germany.

Human research ethics approval number: 13-304

INTRODUCTION

Significant differences exist in the incidence of lower limb amputations worldwide, ranging from 46.1 to 9.600 per 100.000 in the diabetic population and 5.8-31 per 100.000 in the total population (1). The existence of phantom limb pain (PLP) is a major complaint of patients following amputation. Up to 90% of patients after amputation suffer from chronic PLP (2-6), leading to limitations in daily activities and reduced quality of life (2, 7-10). As many patients with amputation live at home (2), there is need for efficient self-management strategies to handle phantom limb pain sustainably. These strategies might increase patient self-efficacy and decrease phantom limb pain and pain-related limitations in daily activities (11-13). Unfortunately, appropriate (self-)management of PLP is still a major challenge. Despite many pharmacological interventions, long-term efficacy of these treatment strategies is lacking (14). Alternative, non-pharmacological interventions such as mental practice or mirror therapy are gaining increased attention in the treatment of phantom limb pain (15-18). The available literature shows good quality of evidence that mirror therapy is effective as an additional intervention in improving recovery of arm function in stroke patients (19, 20). However, the evidence in patients with PLP is still low. In a recent systematic review (20) we showed that to date, only two small randomized controlled trials (RCT) demonstrate that mirror therapy is effective in reducing phantom limb pain (15, 17). A high quality RCT with properly described treatment protocol is missing. Based on our systematic review of treatment protocols showing positive results (20), one could advise that mirror therapy should be conducted with a minimum frequency of one session per day over a period of several

weeks. However, this treatment frequency is often beyond the resources available in clinical practice. In addition, long-term adherence to self-delivered exercises is generally low (21). It has been suggested that additional support can be useful to discuss problems that occur during self-management, to individually modify the treatment program and to increase long-term adherence to treatment (21). The latter can be achieved by using telerehabilitation, which enables remote support of patient's autonomy and monitoring of self-management (22-25). An important element in the development and implementation of telerehabilitation systems is a thorough analysis of user requirements to prevent lack of user acceptance (26-30). Until now, user involvement and participation is often neglected when such applications are designed (28, 29). To date, no telerehabilitation exists, that is tailored to the needs of patients with phantom limb pain and the preferences of physical and occupational therapists who are treating those patients with mirror therapy.

This article describes the study protocol of the randomized controlled study of the PAtient Centred Telerehabilitation (PACT) project (fig. 1).

Objectives

The overall aim of the randomized controlled study is to investigate the effectiveness of mirror therapy supported by telerehabilitation on the intensity, duration and frequency of phantom limb pain and daily activities compared to traditional mirror therapy and usual care without mirror therapy in patients following lower limb amputation (three arms).

In the PACT project we applied a user-centered approach to develop a telerehabilitation for patients with phantom limb pain following lower limb amputation. Figure 1 shows an overview of the different phases within the PACT project. An extensive description of this developing process and results will be described in another publication.

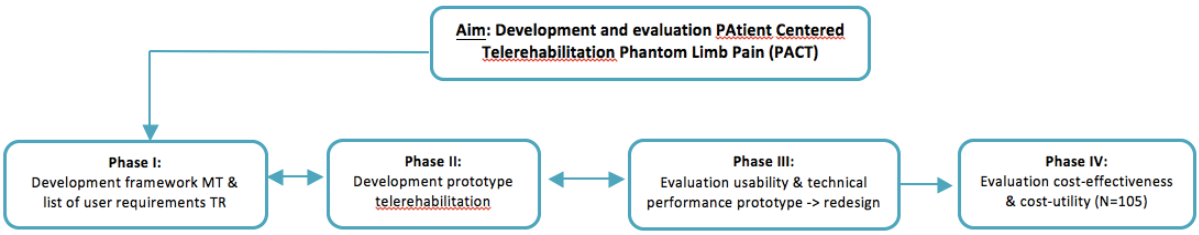

Figure 1. Overview of the different phases within the PACT project.

Research questions

For further information see also figure 2 and table 1.

1) Are there any differences in treatment effect between a 4-weeks intervention using care as usual (group A) and 4-weeks traditional mirror therapy (group B & C) on intensity, duration and frequency of phantom limb pain and pain related limitations in daily activities in patients with phantom limb pain following lower limb amputation?

2) Are there any differences in treatment effect between traditional mirror therapy followed by mirror therapy supported by telerehabilitation (group C) compared to traditional mirror therapy followed by self delivered mirror therapy (group B) and care as usual without traditional mirror therapy (group A) on intensity, duration and frequency of phantom limb pain, pain related limitations in daily activities, pain specific self-efficacy and quality of life?

3) What is the cost-effectiveness and cost-utility of traditional mirror therapy followed by mirror therapy supported by telerehabilitation (group C) compared to traditional mirror therapy followed by self delivered mirror therapy (group B) and care as usual without traditional mirror therapy (group A) from a societal perspective?

METHOD

Design

A three-arm multi-centre randomized controlled trial will be performed involving patients following lower limb amputation from multiple centres (rehabilitation clinics and private practices). Patients will be randomly assigned to one of the three following conditions. A: 4-weeks sensomotor exercises to the intact limb without a

mirror (care as usual) followed by 6 weeks self-delivered care as usual; B: 4-weeks traditional mirror therapy followed by 6-weeks self-delivered mirror therapy without support (experimental condition 1) or C: 4-weeks traditional mirror therapy followed by 6-weeks self-delivered mirror therapy supported by telerehabilitation (experimental condition 2). All baseline measurements (T0) will be obtained after recruitment of participants and before random assignment to either the care as usual or experimental groups (see fig. 2). Endpoints of the trial will be assessed directly after the first four weeks intervention phase (T1), after six weeks of self-management (T2), and at six months follow-up (T3).

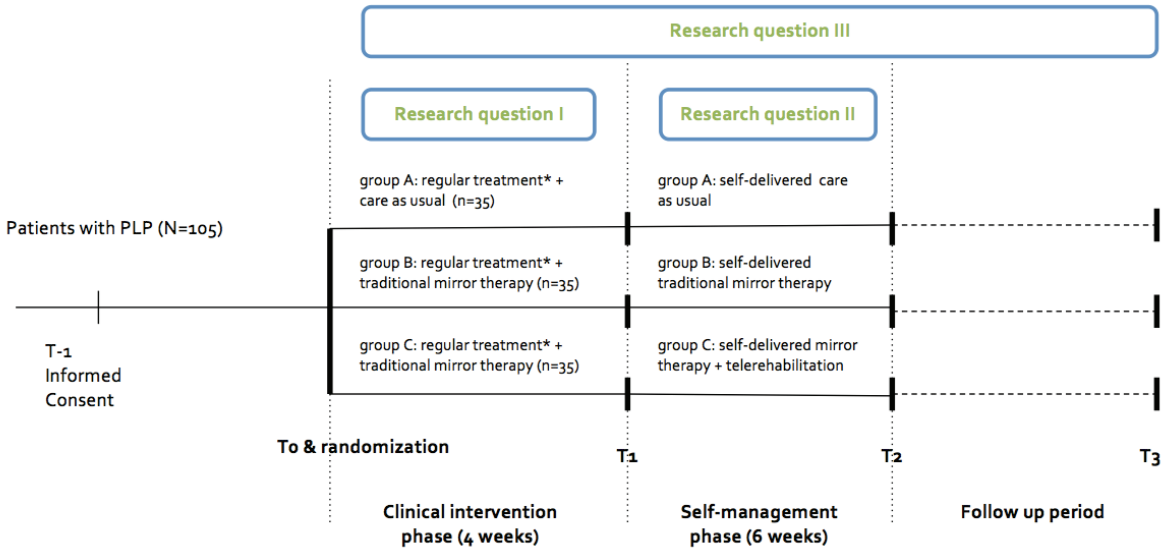

Figure 2. Overview on the study design of the randomized controlled study of the PACT project.

Legend: T-1=1-4 days before T0; T0=baseline; T1= 4 weeks following T0; T2=10 weeks following T0; T3= 6 months following T0; PLP= phantom limb pain

Participants

This trial will commence recruitment in May 2014 and is expected to be completed in July 2015.

Patients after lower limb amputation will be recruited through treating physicians at participating centers or allied health professionals. In addition, confederative centers, patient support groups and online advertisement assist in recruiting eligible participants living at home. To be engaged in this trial, patients have to fulfill the following selection criteria:

a) Lower limb amputation
b) At least since one week constant or intermittent phantom limb pain (PLP) with an average intensity of at least score 3 on the 11-point numeric rating scale (NRS) and a minimum frequency of one episode of PLP per week.
c) Sufficient cognitive, communicative and motor functions to be able to use the telerehabilitation service, to concentrate for at least 15 minutes on the mirror image and to follow instructions and questionnaires; this is based on clinical judgment of recruiting physicians or therapists.

Exclusion criteria:

d) Not able to follow at least 10 individual sessions during the first 4 weeks.
e) Bilateral amputation, severe co-morbidity (e.g. stroke) or pain affecting the intact limb; this prevents engagement in the prescribed exercise programs of the study.
f) Severe psychiatric disorder that precludes the patient from participating in the trial.
g) Intensive course of mirror therapy in the past (> 6 individual sessions during the last three months).

Sample size calculation

The calculation of sample size is based on the primary endpoint, the mean intensity of the last episode of PLP, measured on an 11-point NRS. A mean difference of 2 (sd=2.25) points on the NRS between condition A (control group) and B (traditional mirror therapy) is regarded as a clinically relevant difference (31-33). While assuming an intra-class correlation of 10%, for a power of 80% and a significance level of 0.05, 30 patients are required per condition (34). However, we expect a dropout rate of approximately 20% so we aim to include 35 patients per condition, 105 in total.

Randomization

Participants will be individually randomized per center using a computerized, blocked randomization scheme, with block sizes of six, to achieve an equal distribution of participants across all groups after every sixth patient in each centre. No further

stratification will take place (35). An independent blinded research assistant outside the participating centers will administer the randomization sequence. For every center the randomization scheme and corresponding group allocation will be stored on the personal mobile phone of the research assistant secured by password. Only the administering person and its deputy will have access to the file. After recruitment and baseline measurement, each patient will be registered and the principal investigator (AR) will be informed by phone. The latter will contact the administering person to disclose group allocation and will communicate the assigned treatment to the treating therapist. This randomization procedure will be identical for all participating centers.

Interventions

Participating physicians and therapists will be trained before the beginning of the trial regarding the following topics: (1) selection criteria and process of patient recruitment; (2) aims, design and measurements of the study; (3) content of the interventions. For all interventions a standardized treatment protocol has been developed.

In the rehabilitation clinics all interventions will be given additionally to the regular treatments (‘add-on’). The regular treatment is defined as a multi-professional rehabilitation program according to existing guidelines (36). In the private practices all interventions will be given without any other regular treatment.

Within the clinical intervention phase of four weeks (T0-T1), treatment frequency will account for at least ten individual sessions lasting 30 minutes for every condition. Beside the face-to-face sessions, all patients will be encouraged to conduct exercises on their own as much as they want. Appropriate exercise material and a diary to record treatment frequency will be handed out to every patient. The same therapist will treat patients in the two experimental groups. Another therapist, who does not treat patients from the experimental groups, will treat patients in the control group. During the self-management phase of six weeks (T1-T2) until the follow-up measurement six months after T0 (T3) patients will perform self-delivered exercises as much as they want. Table 1 gives an overview of the content of all interventions used within the RCT.

Table 1. Content of interventions used in this study

Group	Content intervention		
	Clinical intervention phase (T0-T1)	**Self management phase (T1-T2)**	**Follow-up period (T2-T3)**
Control intervention (group A)	Regular treatment* + care as usual	Self-delivered care as usual without support	
Experimental intervention I (group B)	Regular treatment* + traditional mirror therapy	Self-delivered traditional mirror therapy without support	
Experimental intervention II (group C)	Regular treatment* + traditional mirror therapy. Introduction to telerehabilitation during the last week	Self-delivered mirror therapy supported by telerehabilitation	Self-delivered mirror therapy supported by telerehabilitation without contact to therapist

* Applicable to inpatients only

Control intervention (group A)

Patients in the control group will conduct the same sensomotor exercises with the intact limb using the same treatment dose as patients in the traditional mirror therapy group (group B), but without using a mirror (=care as usual). During all exercises patients will observe the movements of the intact limb. At the end of the clinical intervention phase, patients will be encouraged to continue exercises on their own until the follow-up measurement (T3).

Experimental intervention I (group B)

Patients in the first experimental group will receive traditional mirror therapy using sensomotor exercises to the intact limb from the following categories:

a) Observation of various positions in the mirror (creation of the ‘mirror illusion’)

b) basic motor exercises (e.g. flexion-extension movements)

c) sensory stimulation exercises (e.g. using different brushes)

d) functional motor exercises (e.g. grasping balls with the toes)

e) mental practice of phantom exercises using the mirror (e.g. alternately observing movements in the mirror and mentally practicing these movements with the phantom)

In the first sessions the therapist will determine for every patient which exercises are most effective in achieving a vivid sensomotor sensation in the phantom limb. The latter seems to be an important factor regarding the effects of a mirror therapy intervention (37, 38). Subsequently, these exercises will be trained during the

remaining sessions. At the end of the clinical intervention phase (T1), patients will be encouraged to continue mirror therapy on their own until the follow-up measurement (T3).

Experimental intervention II (group C)

The second experimental intervention consists of traditional mirror therapy followed by self-delivered mirror therapy supported by telerehabilitation. During the clinical intervention phase patients will receive the same mirror therapy exercises as patients in group B. In addition, patients will be trained on how to use the telerehabilitation at the end of the clinical intervention phase before discharge. Every patient will be loaned a tablet-PC and a set of training materials for the duration of the self-management phase. The telerehabilitation uses different components:

a) Background information on phantom limb pain and given interventions
b) Monitoring of phantom limb pain (e.g. intensity & frequency of pain)
c) Self delivered exercises to treat phantom limb pain (videos on mirror therapy and mental practice, augmented reality using the tablet-integrated camera, limb laterality recognition training, relaxation exercises)
d) Communication with therapist and other patients suffering from phantom limb pain

At the end of the clinical intervention phase patients will be instructed to use the telerehabilitation as often as they want in the daily situation. During the six-weeks self- management phase (T1-T2) patients can communicate with the treating therapist in case of problems arising with the exercises. During the follow-up period (T2-T3) patients will be allowed to use the telerehabilitation but without support of the treating therapist.

Outcome measures & procedure

The recruiting therapist will assess all outcomes at baseline (T0). All measurements at the end of the intervention and follow-up phases (T1-T3) will be performed by an independent, blinded research assistant. The research assistant will mail all questionnaires to the patients and assist patients by phone in completing the

questionnaires. The assistant will ask patients not to reveal their assigned treatment during the measurement. Table 2 gives an overview of all measurements obtained during this study. As is common in physical therapy interventions, it will not be possible to blind patients or therapists for treatment condition (39).

Table 2. Overview of outcomes, measurement instruments and – moments used in the PACT study

Data	Time point	Aim of measurement
Patient characteristics		
Age, gender, side & level amputation, etc.	T0	Comparison of baseline characteristics
Prognostic variables		
CEQ: Expectancy regarding treatment effect	T0	Prediction of treatment effect
Treatment frequency, prosthesis usage, position of phantom limb, etc.	T0, T1, T2, T3	
Primary outcomes		
11-point NRS: Intensity of PLP	T0, T1, T2, T3	Limitations on 'body functions/structures' level
Frequency & duration of PLP	T0, T1, T2, T3	
Secondary outcomes		
NPSI: Dimensions of PLP	T0, T1, T2, T3	Limitations on 'body functions/structures'
PSFS & PDI: Pain related limitations in daily activities	T0, T1, T2, T3	Limitations on 'activities' level
EQ-5D-5L: Quality of life	T0, T2, T3 T1, T2, T3	Limitations on 'activities' and 'participation' level
GPE: Overall treatment effect	T0, T1, T2, T3	Analysis of environmental factor
FESS: Pain specific self-efficacy		
During intervention period		
Log: Treatment frequency, medication intake	Daily	Monitoring of treatment
Cost questionnaire	T1, T2, T3	Monitoring of direct/indirect costs
Acceptance questionnaire	T2	Assessment of acceptance of telerehabilitation
Co-Interventions, integrity check	T1, T2, T3	Process evaluation

Legend: T-1=1-4 days before T0; T0=baseline; T1= 4 weeks following T0; T2=10 weeks following T0;

T3= 6 months following T0; PLP= phantom limb pain; CEQ: Credibility & expectancy questionnaire; NRS: Numeric rating scale; NPSI: Neuropathic pain symptom inventory; PSFS: Patient specific functional scale; PDI: Pain disability index; EQ-5D-5L: EuroQuol questionnaire; GPE: Global perceived effect scale; FESS: Fragebogen zur Erfassung der schmerzspezifischen Selbstwirksamkeit.

Patient characteristics

At baseline (T0) the following patient characteristics will be assessed: age, gender, educational level, profession and family status. In addition the following variables regarding the amputation will be recorded: side, level, date and reason for amputation, type and frequency of usage of prosthesis, medication and diagnosed neuroma. With respect to the phantom limb the perceived position, size, length and ability to voluntary move the phantom on an 11-point NRS (0=no movement, 10=normal) will be determined. These aspects are thought to be of prognostic value

(38). After randomisation and treatment allocation, patients' treatment expectancy and rationale credibility will be measured with the credibility and expectancy questionnaire (CEQ) (40), as these factors might represent non-specific treatment effects (41). These data will be analysed regarding their prognostic value and to compare characteristics of the three groups at baseline.

Primary outcome measures

The mean intensity of phantom limb pain during the last week will be assessed using an 11-point numeric rating scale (NRS) (0= no pain, 10= pain at its worst). Additionally, the frequency and duration of pain episodes will be scored. The NRS shows good validity and reliability. The minimal clinically relevant difference on the NRS on group level is 2 points (31-33).

Secondary outcome measures

The different dimensions of PLP will be assessed through the German Version of the Neuropathic Pain Symptom Inventory (NPSI-G) (42). The NPSI includes 10 descriptors and two temporal items to discriminate and quantify clinically relevant dimensions of neuropathic pain. Each of the 10 descriptors uses an 11-point NRS (0=no pain, 10=pain at its worst) to score the intensity of the pain description. The NPSI shows good construct validity, high test-retest reliability, is sensitive to change and has been translated into several languages (43, 44).

Pain related limitations in daily activities will be assessed by the German version of the patient specific functional scale (PSFS) (Heldmann, in press). Three, for each individual patient important activities that are hampered due to phantom limb pain will be scored using an 11-point numeric rating scale (NRS) (0=no limitations, 10=not possible to perform activity) (45-47). Sufficient validity, reliability and sensitivity to change have been established in patients with different pain syndromes with a minimal clinically relevant difference of 2 points or 30% on group level (45, 47-49).

Additionally, limitations in daily activities will be assessed by a more generic measure, the German version of the Pain Disability Index (PDI) (50). The degree of limitations in daily activities will be scored on seven topics using an 11-point numeric rating scale (NRS) (0=no limitations, 10=not possible to perform activity). The seven

topics from the PDI will be complemented by two items, sleep and mood, from the brief pain inventory (BPI) (51, 52). These two topics are often affected by phantom limb pain but are insufficiently addressed within the PDI. The BPI uses the same scoring system as the PDI. The two additional items on the BPI will be separately scored and analysed. The PDI has sufficient psychometric properties with a minimal clinically relevant difference of 9 points (53-57).

Quality of Life will be measured on five domains using the German version of the EuroQol Questionnaire (EQ-5D-5L) (58, 59). Each item is scored using a five-point scale (1=no problems, 2=slight problems, 3=moderate problems, 4=severe problems, 5=unable to do/extreme problems). Additionally, the EQ-5D-5L uses a visual analogue scale (VAS) to score overall health (0= worst imaginable health; 100=best imaginable health). Psychometric properties of the EQ-5D-5L are sufficient, except a ceiling effect (59).

Global perceived effect (GPE) of treatment will be rated on a 7-point scale (-3=extreme worsening; +3=extreme improvement) to assess patients' subjective perceptions of recovery. Test-retest reliability of the GPE scale is excellent. However, GPE ratings seem to be strongly influenced by current status (60).

Pain specific self efficacy will be assessed using the German version of the pain self efficacy questionnaire (PSEQ) (61). The questionnaire consists of 10 items on the perceived degree of self-efficacy that can be scored on a 7-point scale (0=not at all confident; 6=completely confident) (62). The PSEQ has good internal consistency and test-retest reliability (61).

Additional variables

Several additional variables will be assessed to analyse feasibility, integrity and compliance of the treatment.

Feasibility & Integrity

At the end of the self-management phase (T2) patients' and therapists' satisfaction and acceptance of the telerehabilitation service will be evaluated with 9 items on an 11-point scale (0=strongly disagree, 10=absolutely agree). The items on acceptance have been derived form the Technology Acceptance Model (TAM) (63, 64) including

questions on intention to use, perceived usefulness, ease of use and application-specific self-efficacy. In order to evaluate integrity of the treatment, all therapists will be encouraged to record any deviation from the treatment protocol, adverse effects or other particularities after every session in a log.
Additional information on co-interventions or medical problems will be registered in a log as well and a standardized drop out evaluation takes place over the study period (T0-T3). An independent research assistant will register reasons for drop out and possible adverse effects if patients give their consent. As our statistical analysis is based on intention to treat, we will ask patients to give consent on registering data after withdrawal.

Compliance

In the telerehabilitation group, software will assess exercise frequency and duration through data logging. In the mirror therapy and control group a log will be used to assess frequency of (self-delivered) exercises. The treating therapist will regularly check these data.

Economic Evaluation

Costs and effects will be evaluated from a societal perspective. In order to assess direct and indirect costs, a cost questionnaire will be used in every group at all measurement moments following baseline (T1-T3). Direct costs include health care utilization in general (e.g. visits to health care providers, drug use) and non-health care costs (e.g. out-of the pocket costs, travel costs or paid and unpaid help). The number of consultations will be multiplied by the cost of each visit to calculate total direct costs. Indirect costs include data from loss of productivity (e.g. illness related absence from paid and unpaid work). Patients will be encouraged to register only resources that are used in relation to phantom limb pain. Costs for development and implementation of the telerehabilitation service will also be calculated.

Data analysis

Demographic data of patients as well as primary and secondary outcomes will be analysed at baseline (T0) on significant differences between the groups. In case of significant differences between groups analysis of covariance will be performed. For

all measurement moments following baseline (T1-T3) mean differences between groups and effect sizes (Cohens' d) will be calculated for the outcome variables. In addition, a repeated measures design will be used with primary and secondary outcomes as dependent variables, group as between-subjects factor and moment of measurement as the within-subjects factor. Prognostic variables will be identified through regression analysis and data from the logs will be analysed qualitatively. A subgroup analysis will be performed on the variables age and gender. Statistical analysis of group differences will be performed according to the intention to treat principle.

In the economic evaluation differences in costs and effects between all groups will be compared using the incremental cost-effectiveness ratio including the net costs per reliable and clinically relevant improved case of pain. The costs and effectiveness of the interventions will be displayed by a cost effectiveness plane. In addition, an incremental cost-utility ratio will be calculated incorporating the net costs per quality adjusted life years (QALY) gained.

Ethical considerations

Before study inclusion, each participant will be sufficiently informed about the study purposes and content by providing an information leaflet. Patients will have sufficient time (at least 2 working days) to think about study participation and to sign informed consent. Table 3 gives an overview of the ethical considerations. The study has been approved by the Ethics committee of the Medical Faculty of Cologne University, Cologne, Germany (approval no. 13-304).

Table 3. Overview of ethical considerations

Ethical aspect	Comment
Are participants sufficiently informed about the study?	Before study inclusion, each participant is sufficiently informed about the study purposes and content by providing an informed consent form. Patients have sufficient time (at least 2 days) to think about study participation and sign informed consent. Patients are free to withdraw from study participation without giving any reason and any consequences on their medical treatment.
What are the additional risks for	The existing literature suggests, that during mirror therapy adverse effects

participants?	(e.g. dizziness, nausea) might occur over a short period of time.
What are the potential benefits for participants?	The treatment can have a positive effect on phantom limb pain, disability and quality of life. Patients are informed about the background of phantom limb pain and are trained in self-management strategies. Participants can get in contact with other patients suffering from phantom limb pain.
What are potential benefits form a societal perspective?	The treatment might induce positive socioeconomic effects. Several publications are submitted and researchers and health care providers are trained regarding research methodology and interventions.
What is the extra burden for participants?	Moderate extra time load through additional measurements not incorporated in usual care and self-delivered exercises.

DISCUSSION

The overall aim of this randomized controlled study is to investigate the effectiveness of mirror therapy supported by telerehabilitation on the intensity, duration and frequency of phantom limb pain and daily activities compared to traditional mirror therapy and care as usual in patients following lower limb amputation.

The available literature shows good quality of evidence that mirror therapy is effective as an additional intervention in improving recovery of arm function in stroke patients (19, 20). However, the evidence in patients with PLP is still low. In this article we describe the design of a three-arm multi-centre randomized controlled trial. Two important research questions are addressed in this study. The first question will address the effects of mirror therapy on phantom limb pain and the second question will determine the additional effects of the telerehabilitation. The latter is an important question as a sufficient frequency of face-to-face visits is not possible given the fact that resources in clinical practice are scarce. In addition, long-term adherence to self-delivered exercises is generally low (21). In the near future, this discrepancy between therapy demand and available resources will even increase due to demographic changes. Growing financial pressures in the health care system and the increase in chronic diseases will shift rehabilitation more and more towards self-management of patients (11-13, 65). Telerehabilitation could help to solve at least some of these problems.

During the preparation of the PACT-project several questions concerning the study design needed to be addressed. In the following section we describe how we dealt with these questions and argue the choices made.

User-centred design

Putting the users at the centre during the development of an e-health application is essential to prevent lack of user acceptance (29). The latter is often neglected when such applications are designed resulting in barriers to deployment (28, 29, 66). In the developmental phase of the PACT study we applied a user-centred design, performing semi-structured interviews to elicit user requirements concerning the content of the telerehabilitation (publication in preparation). This process resulted in a multitude of data making it impossible to integrate all individual requirements into the design of the telerehabilitation. Accordingly, we developed a criterion checklist to structure and prioritize functions which should be integrated within the telerehabilitation and which should not. This checklist contains criteria on 'the available evidence from the literature', whether 'the majority of users mentioned the item', whether there was 'agreement between patients' and therapists' wishes' and 'how technically complex it would be to build the designated function'. Based on these four criteria we graded the priority of the individual requirements enabling us to choose the most important functions that were consequently integrated into the design of the telerehabilitation. After the first prototype was established we tested its usability through an iterative process in which user feedback was continuously incorporated into the design of the revised prototype. In our view this user-centred design was very helpful to facilitate user acceptance of the telerehabilitation.

Justification of the intervention

In our systematic review on the clinical aspects of mirror therapy (20) we showed that there is still no consensus on treatment and patient characteristics when designing a mirror therapy treatment. In order to standardize the intervention we developed a clinical protocol for mirror therapy in stroke patients (67). Development of the protocol was guided by an evidence-based approach in which we merged the best available evidence, clinical experiences of a group of physical and occupational therapists and the preferences and experiences of stroke patients. Using the same approach we have developed a similar protocol for mirror therapy in patients with phantom limb pain (in preparation). This protocol contains the following exercise categories that were also incorporated into the telerehabilitation: creation of a vivid

mirror illusion, basic motor exercises, sensory training, functional motor exercises and mirror-facilitated mental practice. In addition, based on analysis of user requirements, we developed ‘mobile’ interventions that can be used by patients outside their homes without a mirror such as augmented reality using the tablet-integrated camera or limb laterality recognition training (16, 20, 68-73).

In our view, the treatment frequency of at least ten individual sessions in addition to self-delivered exercises during the four weeks clinical intervention phase should be sufficient to achieve a clinically relevant reduction in phantom limb pain (74). This treatment dose was mainly derived from clinical experience and the fact that daily sessions would not be practical for patients living at home. Nevertheless, patients and therapists are encouraged to maximize treatment intensity as far as possible.

The control intervention consists of senso-motor exercises to the intact limb without a mirror (care as usual). This was chosen to ensure sufficient contrast between groups but on the other hand to provide an intervention that also could have at least some effect on phantom limb pain. Results from other studies suggest that treatments to the contralateral limb might also alleviate phantom pain (75-78). However, we believe that the effects of mirror therapy are superior to the control intervention.

Justification of selection criteria

Little is known about which patient characteristics are important when choosing eligible patients for mirror therapy (20). Therefore, we kept selection criteria as pragmatic as possible. Given the fact that a clinically relevant change in pain on the NRS is 2 points (31-33) patients must have a minimum average intensity of phantom limb pain of score 3 on the NRS to be able to detect significant differences between groups. We will exclude patients who followed an intensive course of mirror therapy in the recent past that is defined as more than six individual sessions during the last three months. This cut-off was chosen because in the German health care system mirror therapy as part of physical therapy is often prescribed once with an amount of six sessions. In our view, to achieve sustainable effects through mirror therapy, at least ten sessions are required (74). If a patient followed a more intensive course of mirror therapy before this time frame of three months, we think that possible effects

of mirror therapy in the past have been washed out during this period of three months.

Justification of outcome measures

We tried to follow the recommendations from the Initiative on Methods, Measurements, and Pain Assessment in Clinical trials (IMMPACT) (79) and the guidelines from the Neuropathic Pain Special Interest Group (NeuPSIG) (80) as far as possible when choosing appropriate measurement instruments. We considered choosing additional instruments to monitor physical performance (e.g. activity monitor) (81) but as many patients suffer from PLP in situations in which they are less active (2, 7), we felt that the value of these data could not justify the additional load imposed on patients. Regarding the economic evaluation we deliberated about whether we should use a cost diary or questionnaire in order to measure resource consumption associated with PLP. As questionnaires seem to reproduce similar results as diaries (82), we chose to use a questionnaire because of pragmatic reasons and reduced patient burden.

Final remark

Non-pharmacological interventions such as mirror therapy are getting increased recognition in the treatment of patients with phantom limb pain. We hope that this study will contribute to the body of evidence for mirror therapy in PLP and expand the knowledge on how to deliver mirror therapy in clinical practice and increase compliance after discharge by using information and communication technology.

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Conflict of interest declaration

The authors declare no conflicts of interest.