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Mirror therapy for phantom limb and stump pain: a randomized controlled clinical trial in landmine amputees in Cambodia

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Abstract:	Background and aims: The aim of the study was to examine the effect of mirror and tactile therapy on phantom and stump pain in patients with traumatic amputations, with particular reference to amputees in low-income communities. Methods: The study was conducted with an open, randomized, semi-crossover case-control design in rural Cambodia. A study sample of 45 landmine victims with trans-tibial amputations was allocated to three treatment arms; mirror therapy, tactile therapy, and combined mirror-and-tactile therapy. Non-responders from the mono-therapy interventions were crossed over to the alternative intervention. The intervention consisted of five minutes of treatment every morning and evening for four weeks. Endpoint estimates of phantom limb pain (PLP), stump pain, and physical function were registered three months after the treatment. Results: All three interventions were associated with more that 50% reduction in Visual Analogue Scale (VAS)-rated PLP and stump pain. Combined mirror-tactile treatment had a significantly better effect on PLP and stump pain than mirror or tactile therapy alone. The difference between the three treatment arms were however slight, and hardly of clinical relevance. After treatment, the reduction of pain remained unchanged for an observation period of three months. Conclusions: The study documents that a four-week treatment period with mirror and/or tactile therapy significantly reduces PLP and stump pain after trans-tibial amputations. Implications: The article reports for the first time a randomized controlled trial of mirror therapy in a homogenous sample of persons with traumatic amputations. The findings are of special relevance to amputees in low-resource communities.

The Editor,
Scandinavian Journal of Pain

Dear editor,
We want to thank the journal for a second careful review. The suggestions from the two reviewers are followed.

Reviewer #1
The “OK?” insertions in the Discussion section were hangovers from the language editing previously done by our English colleague; they are now removed.

Reviewer #2
- The suggestion of clarifying the VAS measurements in section 2.3 is followed, VAS ratings now given by centimeters.
- The two sentences on “withdrawals” in section 2.5 are deleted as recommended.
- In section 2.6 the sentence on 95% confidence intervals is revised as proposed, the word “calculated” being deleted.
- In the Results, section 3.3 we have now included 95% CI for differences between the three subsamples. The reviewer again suggests a ladder plot for before-after VAS ratings. However such a two-step ladder will in our opinion not give additional information to findings already reported in Table 3, besides with 15x3 study units the figure would be rather noisy.
- In section 3.1 the sentence on “no significant confounding” is removed as suggested.
- The word “bar” in section 3.2, line 5 was rightly a typo, now corrected.
- We have completed the minor corrections in section 4.1: The sentence on “poorly controlled variables” is deleted. The sentence “the study design made it unlikely that non-specific factors of this kind...” is changed to “the study design made it unlikely that external factors of this kind...” The word “cross-cultural confounders” is substituted by “cross-cultural differences”. And the sentence “We therefore claim that the statistical estimates reported are solid” is deleted.
- We agree that lacking a true control group is a weakness of the study. The sentence suggested by the reviewer is therefore included in the beginning of section 4.2.
- The numbering of the three sections in the Discussion is now corrected.

We want to thank the reviewers for improving our article through a quick and professional editorial process.

Lakselv, Norway, 9 June, 2018

Hans Husum
Author of correspondence

Mirror therapy for phantom limb and stump pain: a randomized controlled clinical trial in landmine amputees in Cambodia

(RCT of mirror therapy for phantom limb pain)

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Reports from the study have not been previously published, neither orally nor in written form.

Abstract

Background and aims: The aim of the study was to examine the effect of mirror and tactile therapy on phantom and stump pain in patients with traumatic amputations, with particular reference to amputees in low-income communities.

Methods: The study was conducted with an open, randomized, semi-crossover case-control design in rural Cambodia. A study sample of 45 landmine victims with trans-tibial amputations was allocated to three treatment arms; mirror therapy, tactile therapy, and combined mirror-and-tactile therapy. Non-responders from the mono-therapy interventions were crossed over to the alternative intervention. The intervention consisted of five minutes of treatment every morning and evening for four weeks. Endpoint estimates of phantom limb pain (PLP), stump pain, and physical function were registered three months after the treatment.

Results: All three interventions were associated with more that 50% reduction in Visual Analogue Scale (VAS)-rated PLP and stump pain. Combined mirror-tactile treatment had a significantly better effect on PLP and stump pain than mirror or tactile therapy alone. The difference between the three treatment arms were however slight, and hardly of clinical relevance. After treatment, the reduction of pain remained unchanged for an observation period of three months.

Conclusions: The study documents that a four-week treatment period with mirror and/or tactile therapy significantly reduces PLP and stump pain after trans-tibial amputations.

Implications: The article reports for the first time a randomized controlled trial of mirror therapy in a homogenous sample of persons with traumatic amputations. The findings are of special relevance to amputees in low-resource communities.

Keywords

Amputations; Cambodia; mirror therapy; phantom limb pain; stump pain; tactile therapy.

1. Introduction

At least 50% of people who undergo amputations suffer from phantom-limb pain (PLP) [1]. PLP can be related to a certain position or movement of the phantom and may be elicited by physical factors like changes in weather or pressure on the amputation stump, and psychological factors like emotional stress)[2]. Stump pain is positively associated with PLP [3]. Several brain imaging studies have confirmed what Melzack hypothesized in 1990, that the brain processes generating the experience of the whole limb endure following amputation [4, 5, 6]. Central changes in numerous brain regions including somatosensory and motor areas seem to be a major determinant of PLP, with both peripheral and psychological factors contributing to the alterations [2, 7]. It is argued that cortical similarities exist between PLP, Complex Regional Pain Syndrome type-1 (CRPS-1), and brachial plexus avulsion. Cortical neglect of the affected limb leads to changes in cortical mapping [8].

In 1992 Ramachandran introduced the use of mirror visual feedback (mirror therapy, M) for the treatment of chronic pain of central origin after stroke [9]. However, review studies conclude that despite support for mirror therapy in the peer-reviewed literature, the bulk of positive data derives from anecdotal reports, constituting weak evidence at best [10]. Tactile treatment (desensitization) has been used in CRPS cases by the present authors and reportedly in other clinics [11]. Desensitization protocols vary, and to our knowledge there are no guidelines or controlled trials on tactile treatment. Because PLP and CRPS seem to have similar alterations in cortical function, tactile treatment was used as an active treatment control in the present trial.

One main reason for surgical amputations in poor countries who have experienced war is the presence of numerous landmines left behind. Landmine victims in low-income remote communities experience PLP and stump pain, with poverty and emotional stress also being contributing factors [12]. In underprivileged communities where the burden of trauma is highest, feasible treatment options are needed. In 2014 a pilot study was done in the catchment area of the present study. By convenience sampling, eighteen land mine victims with below-knee amputations, all with phantom limb pain, used mirror therapy for five minutes twice a day. All participants bar two reported a reduction of phantom pain, less headache, improved sleep, and improvement of function at the conclusion of a three-week treatment period. Three patients also reported improved functional control of the prosthetic limb: “now it feels as if my toes really touch the ground.”

The primary aim of this study was to examine the effect of mirror therapy on phantom and stump pain in patients with traumatic trans-tibial amputation, with particular reference to low-income communities. A secondary aim was to study the duration of the treatment effect for up to three months.

2. Methods

2.1 Study population and design

The study is registered at ClinicalTrials.gov, ID NCT02912975. The study sample was composed of adults who had developed phantom pain secondary to trans-tibial amputations after landmine trauma in rural Cambodia. The study aimed to examine low-cost treatment alternatives for amputees with phantom limb pain (PLP) and amputation stump pain in a low-income community. The study was designed to examine the effects of mirror therapy as monotherapy (M), tactile treatment as monotherapy (T), and combined mirror + tactile treatment (M+T). The effects of the three treatment arms were compared in an open, randomized, semi-crossover study. The duration of all treatment periods was four weeks. Response to treatment was defined as a 33% reduction in VAS -rated PLP. Non-responders to the first-round tactile treatment were crossed over for secondary mirror therapy, and initial non-responders in the mirror group crossed over for secondary tactile treatment. Non-responders to combined M+T treatment during the first-round treatment were excluded from further treatment (figure 1). The semi-crossover design was applied because it is claimed to increase the probability of giving the best treatment when the therapies under study are poorly documented [13, 14].

The responders were observed for three months after the end of treatment. Following treatment they kept the treatment equipment in their home (the mirror and/or a box with utensils for desensitization). During this three-month observation period they were encouraged to repeat the treatment they found most successful if they experienced increasing pain. The study was closed after an end-point evaluation three months after completed treatment.

2.2 Study sample, recruitment and randomization

The study was conducted from May to August 2016 in a remote rural mine-infested area, Samlot, in Battambang Province, Cambodia. Study patients were chosen by the following criteria: age >16 years; unilateral trans-tibial amputation after landmine trauma more than 12 months before entering the study; suffering from phantom limb pain with or without stump pain. Patients were excluded from the study if they had amputation stump anomalies requiring surgical reconstructions such as chronic infections, neuroma or major soft tissue deformities; chronic alcoholism or drug abuse; loss or deformities of limbs other than the present amputation; or mental and/or cognitive disorders rendering self-rating of health unreliable. The study aim and design were publicized in the catchment area by the local health authorities. Trained local physicians screened potential participants regarding inclusion and exclusion criteria.

When the study sample was identified, computer-generated random numbers were used for simple randomization to the M (n=15), T (n=15) and M+T (n=15) subsamples. Randomization was done without stratification regarding the severity of baseline pain. For several reasons, the study could not

be performed blinded: The patients' families and local health workers were mobilized both in treatment and collection of data. There is anyway close contact within rural communities in daily work and social life. Thus the types and effects of treatment could not be hidden between the study patients and the support staff.

2.3 Variables and factors

Before the intervention, the study population was examined for signs of Complex Regional Pain Syndrome (CRPS) by expert clinical examination, using the criteria of the International Association for the study of Pain [15, 16]. The result variables were estimated by self-rating, using a Visual Analogue Score for estimates of phantom limb pain and stump pain. [17] Participants were asked to mark with pen on a horizontal 10 cm line their estimates of mean pain during the previous week. The VAS scores were registered with one decimal. The study sample was categorized in three groups according to the self-rated severity of pain, severe pain defined as VAS >6 cm, moderate pain as VAS 3-6 cm, and mild pain as VAS <3 cm. Data on gender, age, time since the amputation, and the level of the amputation, were collected.

2.4 The interventions

A pain specialist (LD) instructed the Khmer investigators (HSO, YVH) in clinical pain examinations and in the implementation of treatment protocols. All study patients were told that there were changes in the cerebral cortex associated with PLP, and that external sensory stimuli might modify brain imaging due to the plasticity of cortical function. Careful instructions regarding the details of the interventions was given to participants.

Mirror therapy: The patient sits on a chair, both lower limbs bared. A mirror measuring 30 cm x 80 cm is placed between the legs along the trans-tibial amputation stump so that the patient can see the uninjured limb in the mirror while the amputated limb is hidden behind the mirror screen. For five minutes every morning and night the patient fully concentrates on performing slow repeated movements of the foot from a neutral position to maximum dorsal flexion while closely observing the reflected image of the uninjured limb in the mirror.

Tactile treatment: The patient lies on a bed, not watching the stump, just concentrating on feeling the tactile stimuli, while for five minutes every morning and evening a close family member carefully exposes the skin of the medial, frontal, lateral, and dorsal parts of the amputation stump to five different stimuli: a stone, a wooden stick, a soft brush, a soft cloth, and a soft feather. The same sequence of tactile stimuli is applied in all treatment sessions.

Combined mirror and tactile treatment: The mirror and the tactile treatments go on serially, with five minutes for each treatment. If the patient has the mirror therapy before the tactile treatment in the morning, the tactile treatment is done before of the mirror therapy at night.

2.5 Sample size and processing of data

The sample size calculation was based on the distribution of self-rated PLP. A change of VAS rating of 33% was considered to be relevant. Given an assumed standard deviation of VAS rating of 10 %, power at 80%, significance level at 5%, and with a semi-crossover design, 15 patients were included in each of the three treatment arms. Local expert staff monitored compliance by weekly interviews in the Khmer-Khmer language at the home of each study patient**.** The compliance rate was estimated as the rate of actual treatment periods by required treatment periods (two times per day for 28 days). Baseline data for the outcome variables were collected within one week before the commencement of the treatment period, and follow-up data one week after the conclusion of the treatment period. For the first-round non-responders to M or T, a second-round treatment of four weeks with the alternative treatment started within a month after ending the initial treatment. A “drop-out” was a patient who decided to leave for reasons not related to the study and its implementation. There was only one drop-out in the study.

2.6 Statistical platform and ethical considerations

The study sample was analysed at three stages. Firstly, the randomized subsamples were compared at the conclusion of the first-round treatment. Secondly, based on the assumption that a patient exposed to mirror or tactile therapy remains primed by this treatment when later exposed to the alternative treatment, the responders to the second-round of treatment were re-assigned to the M+T group, and the three treatment arms compared in the reclassified study sample. Finally, the differences between baseline and end-point pain after three months were compared between the three subsamples. Continuously and symmetrically distributed variables are expressed by mean values with 95% confidence intervals by using the Student procedure. Proportions are described using exact 95% confidence intervals (95% CI) [18]. Analysis of Variance (ANOVA) was performed for changes within and comparison between the subsamples. Estimates were considered significantly different if the 95% confidence interval for the difference did not contain zero.

The study was approved The Cambodian National Ethics Committee for Health Research, ref. no. 081/2016 NECHR. The data were stored and processed according to ethical permission from the Norwegian Social Science Data Service, ref. no 2015/2193/REK-North.

3. Results

3.1 Study population and randomization

The mean age of the study patients was 55.7 years (SD 6.7); all but one was male. Traumatic amputations had occurred years before (mean 23 years, range 15-32 years). Most patients had undergone only one primary surgical operation, six patients had experienced two primary operations, and one patient three primary operations. The level of tibial amputation varied: 14 patients had amputations through the proximal third of the tibia, 15 had mid-shaft amputations, and 16 patients amputations through the distal third. Pre-intervention clinical screening of the study sample did not reveal any cases of CRPS. The mean baseline levels of pain were high: with PLP, VAS had a mean of7.2 (SD 2.0); with stump pain, VAS had a mean of 8.1 (SD 1.5). Two outliers were identified. One patient reported mild phantom pain but severe baseline stump pain (VAS 8.6). Another patient reported mild phantom and stump pain. The two pain variables were checked across treatment allocation, age, time since the amputation injury, and level of amputation (table 1).

3.2 The first round of treatment

Compliance rates during the first-round treatment were high, with a mean of 89.9% (SD 16.6). In the second week of the initial treatment period, one patient in the treatment group M+T developed a severe soft tissue infection at the amputation stump and dropped out of the study. This left a study sample of 44 patients who completed the initial intervention. At the conclusion of the four-week treatment period, reduced PLP and stump pain were observed in all of the three treatment arms, except for one patient in the M group and one in the T group. The mean reduction in VAS ratings for phantom and limb pain in all three treatment arms was > 50%. No significant differences were observed between the three subsamples (table 2). Reductions in VAS scores were similar for the patients with severe compared to moderate pain.

3.3 The second round of treatment, reclassification of subsamples

Nine non-responders were identified from first round treatment and assigned to a second round of treatment with the alternate therapy. Three of the non-responders were in the M-subsample and five in the T-subsample. Two non-responders refused to undertake further treatment, so the second round of treatment was given to seven patients. The mean delay between the conclusion of round one and start of round two was 33 days (range 19-53). The compliance rate during the round two treatment was 100%. All initial non-responders reacted to the second-round treatment with a reduction in VAS rating of >90 % for phantom as well as stump pain.

The second round patients who had undertaken the two monotherapies sequentially were reclassified to the M+T category, thus making a study sample of 14 M patients, 10 T patients and 20 M+T patients for the main analysis of treatment effects. Table 3 demonstrates a tendency toward better effect of combined mirror-tactile treatment compared to the monotherapies as estimated by percentage reduction in VAS scores. The 95% confidence interval for the difference in percentage PLP reduction between T and M+T was 2.8-20.3; between M and M+T 10.0-8.6; and between M and T -11.5-31.0.

Also regarding stump pain the combined treatment had a slightly better effect than the monotherapies as estimated by percentage VAS reduction, the 95% CI for the difference between T and M+T being 5.0-15.7; between M and M+T 4.9-22.8. No significant difference was found between the monotherapies, the 95% CI for the difference between the M and T subsample regarding percentage VAS reduction being -10.0-17.0.

3.4 Duration of treatment effects

None of the study patients applied tactile or mirror therapy during the post-treatment observation period. All forty-four study patients estimated the levels of pain three months after the conclusion of the treatment by VAS scales. The end-point ratings demonstrated that the intervention had a sustained effect. The changes in VAS rating from the end of the last intervention to evaluation three months later were minimal: For PLP the mean difference in rating was 0.9 (SD 0.8), for stump pain the mean difference was 1.0 (SD 0.9). No significant differences between the three treatment arms were observed regarding how long the treatment effects lasted.

4. Discussion

We report for the first time a randomized controlled clinical trial of mirror and tactile therapy for PLP and stump pain in a homogenous sample of amputees. This study documents a significant and sustained reduction of PLP and stump pain after two brief interventions daily for a four-week treatment period. Treatment effects were as good for patients with moderate PLP as for those who were severe. The majority of the study patients also reported improved well-being and reduced emotional stress ("freshness in the mind", "improved sleep", "less headache"). Mirror therapy (M) combined with simple desensitization (T) had a slightly better effect than M or T as monotherapies. The difference was statistically significant, however not considered to be of clinical importance.

4.1 Limitations to the study

External physical strains and climatic conditions may trigger PLP [2]. As the geographical catchment area of the study was narrow and study patients all poor, hard-working farmers making a living from non-mechanized agricultural labour, we assume that this minimizes any significant influence of uncontrolled external physical variables. As noted earlier, emotional stress may trigger PLP [19] and this was illustrated in the present trial. One of the initial non-responders reacted to a stressful accident to his son with increasing PLP, but one month later responded well to M. Even if experienced local health workers monitored the study patients closely, there may still have been emotional stressors escaping our attention at pre-intervention screening and through the observation period. Attention per se, the experience of being seen and cared for, and also getting some insight into the neurophysiology of PLP may well have had some placebo effect. However, the study design made it unlikely that external factors of this kind should have favored one treatment arm over the other.

There were minor deviations from the trial protocol. One study patient responded poorly to the initial tactile treatment, perhaps because he suffered from a peroneus neuroma not identified at pre-intervention screening. This patient should thus not have been included in the study. In the event he did gain by being included and responded positively to the crossover treatment. Another patient with severe stump pain was erroneously included on the study, despite having mild pre-intervention PLP. However this patient also benefitted from being included, reporting significant stump pain relief after the crossover treatment. Despite a rather uncontrolled study context the compliance rate was generally high. Four of the nine first-round non-responders had to interrupt or reduce the prescribed doses of treatment due to job or family obligations, but still reported significant reductions in pain levels. Chronic pain after landmine amputation is a well-known condition in these Cambodian villages, affecting the entire family and a concern also for neighbors and friends. As the research team explained the physiology of chronic pain and options for treatment, the local community and the family responded positively to the trial. This probably enhanced compliance, though possibly also any placebo effect.

The re-allocation of crossover patients into the M+T subsample could be questioned. Is a patient undergoing simultaneous combined mirror and tactile treatment equivalent to a patient using the

same two interventions sequentially as monotherapy? Based on their firsthand clinical experience and on brain imaging studies, the authors believe that this is so. It is well documented that the central nervous reorganization of cortical patterns after desensitization or mirror therapy is not erased or "washed out" like an analgesic drug [5, 6, 7, 8, 9]. Based on this neurophysiological understanding of cortical plasticity, we assume that the treatment-induced alterations in somatosensory patterns after round one of treatment remained even if the active treatment ended. We therefore hypothesize that a patient undertaking, say, mirror therapy remains primed by the initial treatment when the potentially additive effect of another type of cortical stimulation occurs. Hence, there is evidence to support an analytical approach where the main analysis is done on a sample where the crossover responders have been merged with the subsample initially randomized for combined M+T therapy.

Finally, cross-cultural differences should be considered. Does the concept "pain" carry the same meaning in Khmer and English language? "Pain" in Khmer, "chheu", means physical suffering. However, the term is also used in an abstract sense referring to "the feeling of agony". The Khmer term thus seems to carry the same double meaning as the English term, comprising both effective pain (pain as immediate sensation) and affective pain (what the pain does to me). When explaining the VAS rating to the participants, care was taken to make them understand that the present rating aimed at the strictly physical pain [20].

The semi-crossover design is ethically attractive as the study patients are entitled to alternative potentially effective treatments. It is also a powerful method as it generates data both from intra-unit and between-unit comparisons. The design is powerful also in small numbers of study subjects, and it compensates well for minor bias[13]. Despite the rather uncontrolled study conditions, the study was conducted according to the protocol with just one dropout and without any withdrawals.

4.2 Clinical implications

Even if mirror and tactile stimulation work well as monotherapies, the study suggests the superior effects of a combined approach. This is in line with previous studies recommending multi-disciplinary treatment strategies for PLP, including enhancement of a cognitive understanding of the painful condition [19, 21]. In the present study the intervention did not merely comprise the mechanics per se of mirror and/or tactile stimulation. The understanding of malformed patterns in the brain as the source of pain, and evidence that the cortex can be reorganized and "normalized", were shared with all study patients before and during the treatment period. Further, the weekly visits by research assistants were not value-neutral observations, but allowed trusted and knowledgeable local health workers to encourage the participants and their families to pay careful attention to the therapy sessions and to improve their morale. The Cambodian study was thus not an exercise in "self-delivered home-based mirror therapy" as reported by Darnall [22]. Even if the impact of verbal support and encouragement as an integrated part of the study intervention cannot be validated, the authors hold that such support is an essential condition for effective somatosensory stimulation. Besides, it would be unethical to withhold from the participants our recent and updated understanding

of the plasticity of the central nervous system.

The findings in the Cambodian study are especially relevant for low-resource communities. The burden of trauma hits hardest in low- and middle-income countries [23]. The survivors of atrocities in Central Africa, Gaza and Aleppo do not have access to sophisticated therapeutic interventions for PLP or stump pain. Where poverty and war are endemic, it is difficult to control and reduce the "sympathetic discharge" produced by emotional stress, as recommended by Hagenberg and Carpenter [21]. But even in such underprivileged communities it is undoubtedly possible to relieve chronic pain and improve function by mirror and/or tactile therapy with support from a close friend and/or family. The feasibility of mirror and simple tactile therapy is the main asset of these methods.

The present study does not provide evidence regarding the recommended intensity and duration of the interventions. Comparison with a true control group receiving either no treatment or placebo is lacking. In retrospect most participants reported significant improvement after just two weeks of treatment, but precise data was not collected on personal trajectories of pain during the intervention. Griffin at al report significant reductions of severe PLP after 28 brief treatment sessions [24], which is comparable to the Cambodian experience of a successful treatment protocol of 56 brief interventions over four weeks. As the follow-up period was short, just three months, the long-term effect of the intervention cannot be estimated from the this study. It is well documented, and also reported by several participants in the present study, that stressful events can impact unfavorably on attempts to relieve pain. In order to examine the duration of the treatment effect and identify factors that may trigger PLP relapse, a qualitative study of the participants in this study is now being conducted in Cambodia. The results are pending.

4.3 Conclusion

Four weeks practice of mirror therapy and tactile treatment causes a sustained reduction of PLP and stump pain in the majority of trans-tibial amputees. The most efficient method seems to be simultaneous mirror therapy and tactile treatment, or the two interventions serially. The interventions are simple and cheap, thus appropriate to the treatment of PLP in low-resource communities.

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Authors' statement

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Conflicts of interest: The authors report no conflicts of interest related to the study.

Informed consent: Before signing the informed consent forms, local trusted health workers carefully informed all study participants about the study procedure, data management and of the right to withdraw from the study at any time.

Ethical approval: The study was approved The Cambodian National Ethics Committee for Health Research, ref. no. 081/2016 NECHR. The data were stored and processed according to ethical permission from the Norwegian Social Science Data Service, ref. no 2015/2193/REK-North.

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Figure legend

Figure 1. Flow chart. Non-responders (NR) to the initial mirror or tactile treatment were crossed over to M or T mono-therapy for four weeks. Non-responders to initial combined treatment did not undertake further treatment. All responders (R) were examined three months after the end of treatment.

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Table 1. Baseline characteristics of the three subsamples

	Mirror group n=15	**Tactile group n=15**	**Combination n=15**
Phantom limb pain, mean	6.7 SD 2.7	7.8 SD 1.9	7.34 SD 1.4
Stump pain, mean	8.0 SD 1.7	8.4 SD 1.4	7.9 SD 1.3
Age (years), mean	57.5 SD 6.0	52.0 SD 7.0	57.6 SD 5.7
Years since surgical amputation	23.1 SD 4.7	23.2 SD 4.4	22.5 SD 4.3
Level of amputation, number of patients:			
- proximal 1/3	5	5	4
- mid-shaft	6	4	5
- distal 1/3	4	6	6

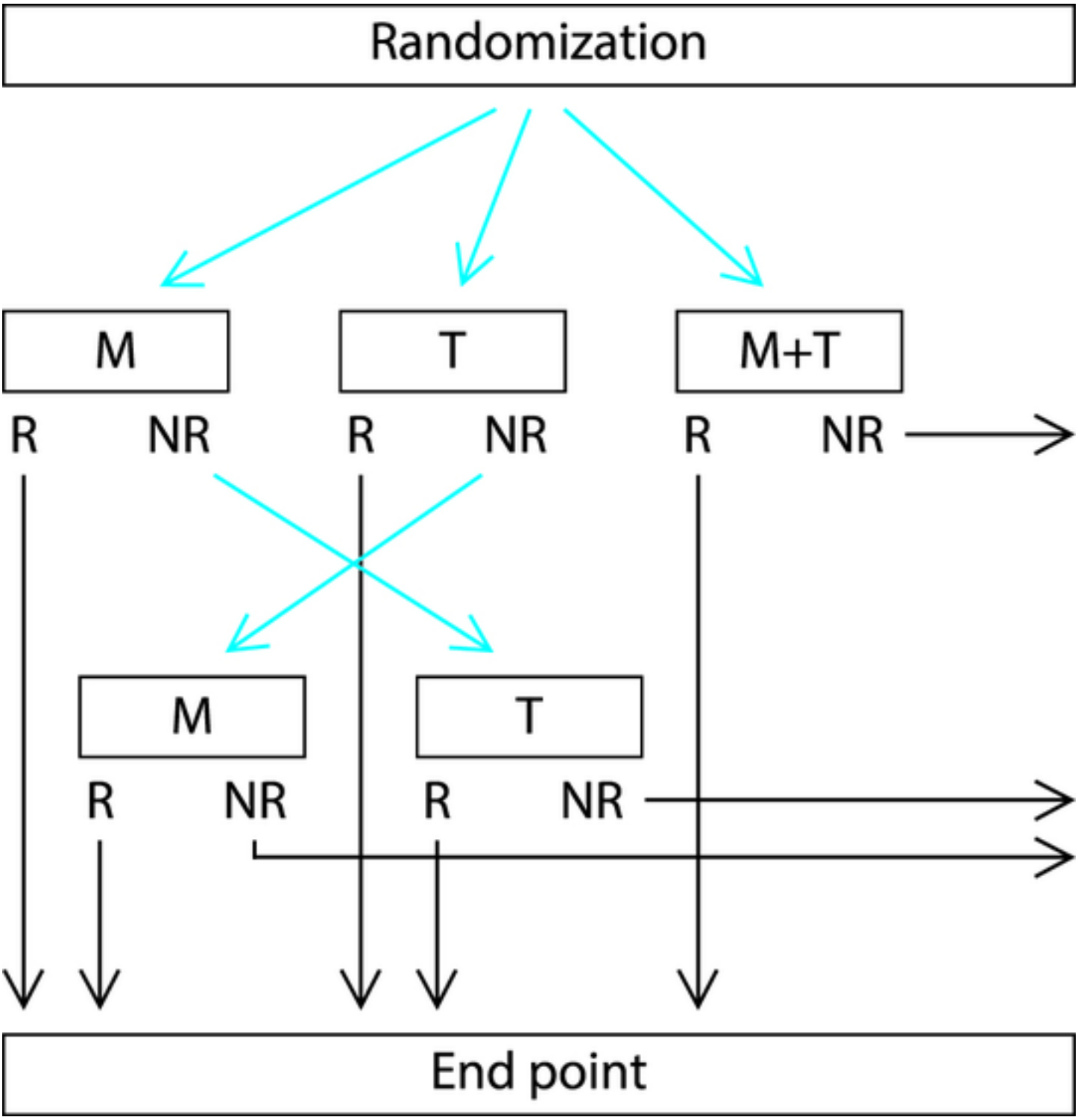
Table

Table 2. First round treatment, effect compared between the three treatment arms

	Mirror Group (n=15)		**Tactile Group (n=15)**		**Combination (n=15)**	
	Mean	95%CI	Mean	95%CI	Mean	95%CI
Phantom pain						
VAS difference	5.0	3.6-6.4	4.3	2.9-5.7	6.2	4.8-7.6
% VAS difference	65.1	50.4-79.8	56.6	41.8-71.2	84.7	69.5-99.9
Stump pain						
VAS difference	6.2	4.9-7.5	4.9	3.6-6.3	6.7	5.4-8.1
% VAS difference	74.7	61.5-87.8	58.6	45.5-71.7	86.2	72.6-99.7

Table 3. Comparison of treatment effects between the three arms, patients reclassified after round-two treatment

	Mirror (n=14)		Tactile (n=10)		Combination (n=20)	
	Mean	95%CI	Mean	95%CI	Mean	95%CI
Phantom Limb Pain						
VAS before treatment	6.6	5.5-7.8	7.6	6.3-8.9	7.1	6.1-8.0
VAS after treatment	1.4	1.1-1.8	1.7	1.3-2.1	0.6	0.3-0.9
VAS difference	5.2	4.0-6.4	5.9	4.5-7.3	6.5	5.5-7.5
% of VAS difference	67.5	57.6-77.5	77.3	65.5-89.1	91.8	83.5-100.2
Stump pain						
VAS before treatment	8.0	7.0-8.9	8.5	7.4-9.6	7.4	6.6-8.2
VAS after treatment	1.5	1.1-1.9	1.6	1.1-2.1	0.6	0.3-0.9
VAS difference	6.4	5.4-7.5	6.9	5.7-8.1	6.8	5.9-7.6
% of VAS difference	77.7	71.2-84.2	81.2	73.5-88.9	91.6	86.1-97.0



Mirror therapy for phantom limb and stump pain: a randomized controlled clinical trial in landmine amputees in Cambodia

(RCT of mirror therapy for phantom limb pain)

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Abstract

Background and aims: The aim of the study was to examine the effect of mirror and tactile therapy on phantom and stump pain in patients with traumatic amputations, with particular reference to amputees in low-income communities.

Methods: The study was conducted with an open, randomized, semi-crossover case-control design in rural Cambodia. A study sample of 45 landmine victims with trans-tibial amputations was allocated to three treatment arms; mirror therapy, tactile therapy, and combined mirror-and-tactile therapy. Non-responders from the mono-therapy interventions were crossed over to the alternative intervention. The intervention consisted of five minutes of treatment every morning and evening for four weeks. Endpoint estimates of phantom limb pain (PLP), stump pain, and physical function were registered three months after the treatment.

Results: All three interventions were associated with more that 50% reduction in Visual Analogue Scale (VAS)-rated PLP and stump pain. Combined mirror-tactile treatment had a significantly better effect on PLP and stump pain than mirror or tactile therapy alone. The difference between the three treatment arms were however slight, and hardly of clinical relevance. After treatment, the reduction of pain remained unchanged for an observation period of three months.

Conclusions: The study documents that a four-week treatment period with mirror and/or tactile therapy significantly reduces PLP and stump pain after trans-tibial amputations.

Implications: The article reports for the first time a randomized controlled trial of mirror therapy in a homogenous sample of persons with traumatic amputations. The findings are of special relevance to amputees in low-resource communities.

Keywords

Amputations; Cambodia; mirror therapy; phantom limb pain; stump pain; tactile therapy.

1. Introduction

At least 50% of people who undergo amputations suffer from phantom-limb pain (PLP) [1]. PLP can be related to a certain position or movement of the phantom and may be elicited by physical factors like changes in weather or pressure on the amputation stump, and psychological factors like emotional stress)[2]. Stump pain is positively associated with PLP [3]. Several brain imaging studies have confirmed what Melzack hypothesized in 1990, that the brain processes generating the experience of the whole limb endure following amputation [4, 5, 6]. Central changes in numerous brain regions including somatosensory and motor areas seem to be a major determinant of PLP, with both peripheral and psychological factors contributing to the alterations [2, 7]. It is argued that cortical similarities exist between PLP, Complex Regional Pain Syndrome type-1 (CRPS-1), and brachial plexus avulsion. Cortical neglect of the affected limb leads to changes in cortical mapping [8].

In 1992 Ramachandran introduced the use of mirror visual feedback (mirror therapy, M) for the treatment of chronic pain of central origin after stroke [9]. However, review studies conclude that despite support for mirror therapy in the peer-reviewed literature, the bulk of positive data derives from anecdotal reports, constituting weak evidence at best [10]. Tactile treatment (desensitization) has been used in CRPS cases by the present authors and reportedly in other clinics [11]. Desensitization protocols vary, and to our knowledge there are no guidelines or controlled trials on tactile treatment. Because PLP and CRPS seem to have similar alterations in cortical function, tactile treatment was used as an active treatment control in the present trial.

One main reason for surgical amputations in poor countries who have experienced war is the presence of numerous landmines left behind. Landmine victims in low-income remote communities experience PLP and stump pain, with poverty and emotional stress also being contributing factors [12]. In underprivileged communities where the burden of trauma is highest, feasible treatment options are needed. In 2014 a pilot study was done in the catchment area of the present study. By convenience sampling, eighteen land mine victims with below-knee amputations, all with phantom limb pain, used mirror therapy for five minutes twice a day. All participants bar two reported a reduction of phantom pain, less headache, improved sleep, and improvement of function at the conclusion of a three-week treatment period. Three patients also reported improved functional control of the prosthetic limb: “now it feels as if my toes really touch the ground.”

The primary aim of this study was to examine the effect of mirror therapy on phantom and stump pain in patients with traumatic trans-tibial amputation, with particular reference to low-income communities. A secondary aim was to study the duration of the treatment effect for up to three months.

2. Methods

2.1 Study population and design

The study is registered at ClinicalTrials.gov, ID NCT02912975. The study sample was composed of adults who had developed phantom pain secondary to trans-tibial amputations after landmine trauma in rural Cambodia. The study aimed to examine low-cost treatment alternatives for amputees with phantom limb pain (PLP) and amputation stump pain in a low-income community. The study was designed to examine the effects of mirror therapy as monotherapy (M), tactile treatment as monotherapy (T), and combined mirror + tactile treatment (M+T). The effects of the three treatment arms were compared in an open, randomized, semi-crossover study. The duration of all treatment periods was four weeks. Response to treatment was defined as a 33% reduction in VAS -rated PLP. Non-responders to the first-round tactile treatment were crossed over for secondary mirror therapy, and initial non-responders in the mirror group crossed over for secondary tactile treatment. Non-responders to combined M+T treatment during the first-round treatment were excluded from further treatment (figure 1). The semi-crossover design was applied because it is claimed to increase the probability of giving the best treatment when the therapies under study are poorly documented [13, 14].

The responders were observed for three months after the end of treatment. Following treatment they kept the treatment equipment in their home (the mirror and/or a box with utensils for desensitization). During this three-month observation period they were encouraged to repeat the treatment they found most successful if they experienced increasing pain. The study was closed after an end-point evaluation three months after completed treatment.

2.2 Study sample, recruitment and randomization

The study was conducted from May to August 2016 in a remote rural mine-infested area, Samlot, in Battambang Province, Cambodia. Study patients were chosen by the following criteria: age >16 years; unilateral trans-tibial amputation after landmine trauma more than 12 months before entering the study; suffering from phantom limb pain with or without stump pain. Patients were excluded from the study if they had amputation stump anomalies requiring surgical reconstructions such as chronic infections, neuroma or major soft tissue deformities; chronic alcoholism or drug abuse; loss or deformities of limbs other than the present amputation; or mental and/or cognitive disorders rendering self-rating of health unreliable. The study aim and design were publicized in the catchment area by the local health authorities. Trained local physicians screened potential participants regarding inclusion and exclusion criteria.

When the study sample was identified, computer-generated random numbers were used for simple randomization to the M (n=15), T (n=15) and M+T (n=15) subsamples. Randomization was done without stratification regarding the severity of baseline pain. For several reasons, the study could not

be performed blinded: The patients' families and local health workers were mobilized both in treatment and collection of data. There is anyway close contact within rural communities in daily work and social life. Thus the types and effects of treatment could not be hidden between the study patients and the support staff.

2.3 Variables and factors

Before the intervention, the study population was examined for signs of Complex Regional Pain Syndrome (CRPS) by expert clinical examination, using the criteria of the International Association for the study of Pain [15, 16]. The result variables were estimated by self-rating, using a Visual Analogue Score for estimates of phantom limb pain and stump pain. [17] Participants were asked to mark with pen on a horizontal 10 cm line their estimates of mean pain during the previous week. The VAS scores were registered with one decimal. The study sample was categorized in three groups according to the self-rated severity of pain, severe pain defined as VAS >6 cm, moderate pain as VAS 3-6 cm, and mild pain as VAS <3 cm. Data on gender, age, time since the amputation, and the level of the amputation, were collected.

2.4 The interventions

A pain specialist (LD) instructed the Khmer investigators (HSO, YVH) in clinical pain examinations and in the implementation of treatment protocols. All study patients were told that there were changes in the cerebral cortex associated with PLP, and that external sensory stimuli might modify brain imaging due to the plasticity of cortical function. Careful instructions regarding the details of the interventions was given to participants.

Mirror therapy: The patient sits on a chair, both lower limbs bared. A mirror measuring 30 cm x 80 cm is placed between the legs along the trans-tibial amputation stump so that the patient can see the uninjured limb in the mirror while the amputated limb is hidden behind the mirror screen. For five minutes every morning and night the patient fully concentrates on performing slow repeated movements of the foot from a neutral position to maximum dorsal flexion while closely observing the reflected image of the uninjured limb in the mirror.

Tactile treatment: The patient lies on a bed, not watching the stump, just concentrating on feeling the tactile stimuli, while for five minutes every morning and evening a close family member carefully exposes the skin of the medial, frontal, lateral, and dorsal parts of the amputation stump to five different stimuli: a stone, a wooden stick, a soft brush, a soft cloth, and a soft feather. The same sequence of tactile stimuli is applied in all treatment sessions.

Combined mirror and tactile treatment: The mirror and the tactile treatments go on serially, with five minutes for each treatment. If the patient has the mirror therapy before the tactile treatment in the morning, the tactile treatment is done before of the mirror therapy at night.

2.5 Sample size and processing of data

The sample size calculation was based on the distribution of self-rated PLP. A change of VAS rating of 33% was considered to be relevant. Given an assumed standard deviation of VAS rating of 10 %, power at 80%, significance level at 5%, and with a semi-crossover design, 15 patients were included in each of the three treatment arms. Local expert staff monitored compliance by weekly interviews in the Khmer-Khmer language at the home of each study patient**.** The compliance rate was estimated as the rate of actual treatment periods by required treatment periods (two times per day for 28 days). Baseline data for the outcome variables were collected within one week before the commencement of the treatment period, and follow-up data one week after the conclusion of the treatment period. For the first-round non-responders to M or T, a second-round treatment of four weeks with the alternative treatment started within a month after ending the initial treatment. A “drop-out” was a patient who decided to leave for reasons not related to the study and its implementation. There was only one drop-out in the study.

2.6 Statistical platform and ethical considerations

The study sample was analysed at three stages. Firstly, the randomized subsamples were compared at the conclusion of the first-round treatment. Secondly, based on the assumption that a patient exposed to mirror or tactile therapy remains primed by this treatment when later exposed to the alternative treatment, the responders to the second-round of treatment were re-assigned to the M+T group, and the three treatment arms compared in the reclassified study sample. Finally, the differences between baseline and end-point pain after three months were compared between the three subsamples. Continuously and symmetrically distributed variables are expressed by mean values with 95% confidence intervals by using the Student procedure. Proportions are described using exact 95% confidence intervals (95% CI) [18]. Analysis of Variance (ANOVA) was performed for changes within and comparison between the subsamples. Estimates were considered significantly different if the 95% confidence interval for the difference did not contain zero.

The study was approved The Cambodian National Ethics Committee for Health Research, ref. no. 081/2016 NECHR. The data were stored and processed according to ethical permission from the Norwegian Social Science Data Service, ref. no 2015/2193/REK-North.

3. Results

3.1 Study population and randomization

The mean age of the study patients was 55.7 years (SD 6.7); all but one was male. Traumatic amputations had occurred years before (mean 23 years, range 15-32 years). Most patients had undergone only one primary surgical operation, six patients had experienced two primary operations, and one patient three primary operations. The level of tibial amputation varied: 14 patients had amputations through the proximal third of the tibia, 15 had mid-shaft amputations, and 16 patients amputations through the distal third. Pre-intervention clinical screening of the study sample did not reveal any cases of CRPS. The mean baseline levels of pain were high: with PLP, VAS had a mean of7.2 (SD 2.0); with stump pain, VAS had a mean of 8.1 (SD 1.5). Two outliers were identified. One patient reported mild phantom pain but severe baseline stump pain (VAS 8.6). Another patient reported mild phantom and stump pain. The two pain variables were checked across treatment allocation, age, time since the amputation injury, and level of amputation (table 1).

3.2 The first round of treatment

Compliance rates during the first-round treatment were high, with a mean of 89.9% (SD 16.6). In the second week of the initial treatment period, one patient in the treatment group M+T developed a severe soft tissue infection at the amputation stump and dropped out of the study. This left a study sample of 44 patients who completed the initial intervention. At the conclusion of the four-week treatment period, reduced PLP and stump pain were observed in all of the three treatment arms, except for one patient in the M group and one in the T group. The mean reduction in VAS ratings for phantom and limb pain in all three treatment arms was > 50%. No significant differences were observed between the three subsamples (table 2). Reductions in VAS scores were similar for the patients with severe compared to moderate pain.

3.3 The second round of treatment, reclassification of subsamples

Nine non-responders were identified from first round treatment and assigned to a second round of treatment with the alternate therapy. Three of the non-responders were in the M-subsample and five in the T-subsample. Two non-responders refused to undertake further treatment, so the second round of treatment was given to seven patients. The mean delay between the conclusion of round one and start of round two was 33 days (range 19-53). The compliance rate during the round two treatment was 100%. All initial non-responders reacted to the second-round treatment with a reduction in VAS rating of >90 % for phantom as well as stump pain.

The second round patients who had undertaken the two monotherapies sequentially were reclassified to the M+T category, thus making a study sample of 14 M patients, 10 T patients and 20 M+T patients for the main analysis of treatment effects. Table 3 demonstrates a tendency toward better effect of combined mirror-tactile treatment compared to the monotherapies as estimated by percentage reduction in VAS scores. The 95% confidence interval for the difference in percentage PLP reduction between T and M+T was 2.8-20.3; between M and M+T 10.0-8.6; and between M and T -11.5-31.0.

Also regarding stump pain the combined treatment had a slightly better effect than the monotherapies as estimated by percentage VAS reduction, the 95% CI for the difference between T and M+T being 5.0-15.7; between M and M+T 4.9-22.8. No significant difference was found between the monotherapies, the 95% CI for the difference between the M and T subsample regarding percentage VAS reduction being -10.0-17.0.

3.4 Duration of treatment effects

None of the study patients applied tactile or mirror therapy during the post-treatment observation period. All forty-four study patients estimated the levels of pain three months after the conclusion of the treatment by VAS scales. The end-point ratings demonstrated that the intervention had a sustained effect. The changes in VAS rating from the end of the last intervention to evaluation three months later were minimal: For PLP the mean difference in rating was 0.9 (SD 0.8), for stump pain the mean difference was 1.0 (SD 0.9). No significant differences between the three treatment arms were observed regarding how long the treatment effects lasted.

4. Discussion

We report for the first time a randomized controlled clinical trial of mirror and tactile therapy for PLP and stump pain in a homogenous sample of amputees. This study documents a significant and sustained reduction of PLP and stump pain after two brief interventions daily for a four-week treatment period. Treatment effects were as good for patients with moderate PLP as for those who were severe. The majority of the study patients also reported improved well-being and reduced emotional stress ("freshness in the mind", "improved sleep", "less headache"). Mirror therapy (M) combined with simple desensitization (T) had a slightly better effect than M or T as monotherapies. The difference was statistically significant, however not considered to be of clinical importance.

4.1 Limitations to the study

External physical strains and climatic conditions may trigger PLP [2]. As the geographical catchment area of the study was narrow and study patients all poor, hard-working farmers making a living from non-mechanized agricultural labour, we assume that this minimizes any significant influence of uncontrolled external physical variables. As noted earlier, emotional stress may trigger PLP [19] and this was illustrated in the present trial. One of the initial non-responders reacted to a stressful accident to his son with increasing PLP, but one month later responded well to M. Even if experienced local health workers monitored the study patients closely, there may still have been emotional stressors escaping our attention at pre-intervention screening and through the observation period. Attention per se, the experience of being seen and cared for, and also getting some insight into the neurophysiology of PLP may well have had some placebo effect. However, the study design made it unlikely that external factors of this kind should have favored one treatment arm over the other.

There were minor deviations from the trial protocol. One study patient responded poorly to the initial tactile treatment, perhaps because he suffered from a peroneus neuroma not identified at pre-intervention screening. This patient should thus not have been included in the study. In the event he did gain by being included and responded positively to the crossover treatment. Another patient with severe stump pain was erroneously included on the study, despite having mild pre-intervention PLP. However this patient also benefitted from being included, reporting significant stump pain relief after the crossover treatment. Despite a rather uncontrolled study context the compliance rate was generally high. Four of the nine first-round non-responders had to interrupt or reduce the prescribed doses of treatment due to job or family obligations, but still reported significant reductions in pain levels. Chronic pain after landmine amputation is a well-known condition in these Cambodian villages, affecting the entire family and a concern also for neighbors and friends. As the research team explained the physiology of chronic pain and options for treatment, the local community and the family responded positively to the trial. This probably enhanced compliance, though possibly also any placebo effect.

The re-allocation of crossover patients into the M+T subsample could be questioned. Is a patient undergoing simultaneous combined mirror and tactile treatment equivalent to a patient using the

same two interventions sequentially as monotherapy? Based on their firsthand clinical experience and on brain imaging studies, the authors believe that this is so. It is well documented that the central nervous reorganization of cortical patterns after desensitization or mirror therapy is not erased or "washed out" like an analgesic drug [5, 6, 7, 8, 9]. Based on this neurophysiological understanding of cortical plasticity, we assume that the treatment-induced alterations in somatosensory patterns after round one of treatment remained even if the active treatment ended. We therefore hypothesize that a patient undertaking, say, mirror therapy remains primed by the initial treatment when the potentially additive effect of another type of cortical stimulation occurs. Hence, there is evidence to support an analytical approach where the main analysis is done on a sample where the crossover responders have been merged with the subsample initially randomized for combined M+T therapy.

Finally, cross-cultural differences should be considered. Does the concept "pain" carry the same meaning in Khmer and English language? "Pain" in Khmer, "chheu", means physical suffering. However, the term is also used in an abstract sense referring to "the feeling of agony". The Khmer term thus seems to carry the same double meaning as the English term, comprising both effective pain (pain as immediate sensation) and affective pain (what the pain does to me). When explaining the VAS rating to the participants, care was taken to make them understand that the present rating aimed at the strictly physical pain [20].

The semi-crossover design is ethically attractive as the study patients are entitled to alternative potentially effective treatments. It is also a powerful method as it generates data both from intra-unit and between-unit comparisons. The design is powerful also in small numbers of study subjects, and it compensates well for minor bias[13]. Despite the rather uncontrolled study conditions, the study was conducted according to the protocol with just one dropout and without any withdrawals.

4.2 Clinical implications

Even if mirror and tactile stimulation work well as monotherapies, the study suggests the superior effects of a combined approach. This is in line with previous studies recommending multi-disciplinary treatment strategies for PLP, including enhancement of a cognitive understanding of the painful condition [19, 21]. In the present study the intervention did not merely comprise the mechanics per se of mirror and/or tactile stimulation. The understanding of malformed patterns in the brain as the source of pain, and evidence that the cortex can be reorganized and "normalized", were shared with all study patients before and during the treatment period. Further, the weekly visits by research assistants were not value-neutral observations, but allowed trusted and knowledgeable local health workers to encourage the participants and their families to pay careful attention to the therapy sessions and to improve their morale. The Cambodian study was thus not an exercise in "self-delivered home-based mirror therapy" as reported by Darnall [22]. Even if the impact of verbal support and encouragement as an integrated part of the study intervention cannot be validated, the authors hold that such support is an essential condition for effective somatosensory stimulation. Besides, it would be unethical to withhold from the participants our recent and updated understanding

of the plasticity of the central nervous system.

The findings in the Cambodian study are especially relevant for low-resource communities. The burden of trauma hits hardest in low- and middle-income countries [23]. The survivors of atrocities in Central Africa, Gaza and Aleppo do not have access to sophisticated therapeutic interventions for PLP or stump pain. Where poverty and war are endemic, it is difficult to control and reduce the "sympathetic discharge" produced by emotional stress, as recommended by Hagenberg and Carpenter [21]. But even in such underprivileged communities it is undoubtedly possible to relieve chronic pain and improve function by mirror and/or tactile therapy with support from a close friend and/or family. The feasibility of mirror and simple tactile therapy is the main asset of these methods.

The present study does not provide evidence regarding the recommended intensity and duration of the interventions. Comparison with a true control group receiving either no treatment or placebo is lacking. In retrospect most participants reported significant improvement after just two weeks of treatment, but precise data was not collected on personal trajectories of pain during the intervention. Griffin at al report significant reductions of severe PLP after 28 brief treatment sessions [24], which is comparable to the Cambodian experience of a successful treatment protocol of 56 brief interventions over four weeks. As the follow-up period was short, just three months, the long-term effect of the intervention cannot be estimated from the this study. It is well documented, and also reported by several participants in the present study, that stressful events can impact unfavorably on attempts to relieve pain. In order to examine the duration of the treatment effect and identify factors that may trigger PLP relapse, a qualitative study of the participants in this study is now being conducted in Cambodia. The results are pending.

4.3 Conclusion

Four weeks practice of mirror therapy and tactile treatment causes a sustained reduction of PLP and stump pain in the majority of trans-tibial amputees. The most efficient method seems to be simultaneous mirror therapy and tactile treatment, or the two interventions serially. The interventions are simple and cheap, thus appropriate to the treatment of PLP in low-resource communities.

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Authors' statement

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Conflicts of interest: The authors report no conflicts of interest related to the study.

Informed consent: Before signing the informed consent forms, local trusted health workers carefully informed all study participants about the study procedure, data management and of the right to withdraw from the study at any time.

Ethical approval: The study was approved The Cambodian National Ethics Committee for Health Research, ref. no. 081/2016 NECHR. The data were stored and processed according to ethical permission from the Norwegian Social Science Data Service, ref. no 2015/2193/REK-North.

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Figure legend

Figure 1. Flow chart. Non-responders (NR) to the initial mirror or tactile treatment were crossed over to M or T mono-therapy for four weeks. Non-responders to initial combined treatment did not undertake further treatment. All responders (R) were examined three months after the end of treatment.