Efficacy of mirror therapy and virtual reality therapy in alleviating phantom limb pain: a meta-analysis and systematic review

Christopher Rajendram BSc[1], Gie Ken-Dror PhD[1], Thang Han PhD[1,2], Pankaj Sharma MD, PhD, FRCP[1,3,*]

[1]Institute of Cardiovascular Research, Royal Holloway University of London (ICR2UL), London TW20 0EX, UK.

[2]Department of Endocrinology, Ashford and St Peter's Hospitals NHS Foundation Trust, Surrey, UK.

[3]Department of Neurology, Imperial College Healthcare NHS Trust, UK.

***Corresponding author**: Prof. Pankaj Sharma

Institute of Cardiovascular Research Royal Holloway, University of London (ICR2UL), London TW20 0EX, UK.

Tel: +44 1784 443 807

Email: pankaj.sharma@rhul.ac.uk

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Abbreviations: PLP, phantom limb pain; VR, virtual reality; VAS, visual analogue score; MD, mean difference; SD, standard deviation; CI, confidence interval; HMD, head-mounted display.

Key messages

- Phantom limb pain (PLP) is a potentially debilitating form of chronic pain, the prevalence ranges from 50% to 90%, likely affecting around 65 to 115 million people worldwide.
- Mirror therapy and Virtual Reality (VR) are two commonly used treatments. Mirror therapy was originally developed in the mid-1990s, Virtual reality (VR) is a more recent therapy.
- Mirror therapy and VR therapy significantly reduced pain. Both treatments have similar effect sizes, with more than doubling the likelihood of decreasing mean PLP levels.
- Both mirror therapy and VR are efficacious in alleviating PLP, with neither being more effective than the other.

ABSTRACT

Background: Amputations result from trauma, war, conflict, vascular diseases, and cancer. Phantom limb pain (PLP) is a potentially debilitating form of chronic pain affecting around 100 million amputees across the world. Mirror therapy and Virtual Reality (VR) are two commonly used treatments, and we evaluated their respective success rates.

Methods: A meta-analysis and systematic review was undertaken to investigate mirror therapy and virtual reality (VR) in their ability to reduce pain levels. A mean difference model to compare group pain levels pre- and post-treatment via aggregating these results from numerous similar studies was employed. Meta-analysis was conducted using RevMan (v5.4) and expressed in mean difference (MD) for Visual Analogue Score (VAS).

Results: A total of 15 studies met our search criteria; they consisted of 8 mirror therapy with 214 participants and 7 VR including 86 participants, totalling 300 participants. Mean age ranged between 36-63 years, 77% male, of which 61% were lower body amputees. Both led to a VAS reduction (mirror therapy mean reduction VAS score were 2.54, 95%CI 1.42-3.66; $P<0.001$; VR 2.24, 95%CI 1.28-3.20; $P<0.001$). There was no statistically significant difference in pain alleviation between mirror therapy and VR ($P=0.69$).

Conclusions: Mirror therapy and VR are both equally efficacious in alleviating PLP, but neither is more effective than the other. However, due to small sample size and limited number of studies, factors such as gender, cause of amputation, site of limb loss or length of time from amputation, which may influence treatment success could not be explored.

INTRODUCTION

Phantom limb pain (PLP) refers to ongoing painful sensations that seem to be coming from the part of the amputated limb and is described as burning, stinging, aching, and piercing pain[1]. The prevalence of PLP ranges from 50%[2] to 90%[3], likely affecting around 65 to 115 million people worldwide. In 2017, the number of amputees living around the world due to trauma alone was estimated to be 57.7 million[4]. As trauma is said to be the cause of roughly 45% of amputations[5], this gives a total global estimate of about 128 million amputees. Trauma, including from wars and conflicts, is the second leading cause of amputation after vascular diseases (diabetes, peripheral arterial disease, limb-threatening ischemia), while cancerous tumours are the most common cause of amputation.

Mirror therapy was originally developed in the mid-1990s and simply uses a mirror placed in the sagittal plane just in front of the patient. When in an appropriate position, the patient places their intact limb adjacent to the mirror superimposing onto the missing limb, thereby on moving the intact limb giving the visual illusion of the missing limb mimicking in an identical way. The primary physiological pathway which is thought to be behind the effect of mirror therapy is that this visual trick acts to reverse the restructuring of the cortical map of the primary somatosensory cortex, shown via functional magnetic resonance imaging (fMRI) data[6].

Virtual reality (VR) is a more recent therapy allowing the patient to immerse in a setting where their missing limb is digitally rendered in to give the illusion of it being there, ideally with a head-mounted display (HMD) with screens just in front of their eyes to facilitate this immersion. VR systems like these in theory provide additional benefits over mirror therapy. For example, VR provides more ‘degrees of freedom’ in manipulating the phantom limb because with mirror therapy the intact and phantom limbs will only ever move simultaneously.

The VR system can incorporate time delays coded to give the illusion of the virtual limb moving independently of the intact one. Additionally, mirror therapy inherently cannot be a functioning treatment for bilateral amputees as it requires an intact limb to be reflected. As VR systems can operate just by tracking the motion of the patient's stump alone, they are not constraint by this limitation[7].

Military amputees are known to suffer from PLP therefore, it is important to understand whether any of these treatment options are beneficial to military veterans. For this reason, we conducted a meta-analysis and systematic review of all studies of mirror therapy or VR on amputees to determine which treatment option is most effective in reducing PLP.

METHODS

Search criteria

Two investigators followed PRISMA and Cochrane guidelines, and independently searched MEDLINE and Google Scholar up to March 2021 using the key terms: *clinical trial*, *randomized controlled trial*, *phantom limb pain*, *phantom pain*, *mirror therapy*, and *VR*. All languages were searched. Boolean operators “AND” and “OR” were used to combine search terms. Relevant studies were hand-searched within these references.

Inclusion Criteria

Randomised controlled trials or cohort studies directly investigating the effect of mirror therapy or VR on PLP with no restrictions on the anatomical location of affected limb (e.g., uni- or bi-lateral, upper- or lower-limb); a quantitative Visual Analogue Score (VAS) measurement of pain levels before and after therapy. The VAS uses a score between 0 and 10 to quantify pain[8].

Outcome measures

Primary outcome was assessed as a change in VAS scores as an indicator of whether the therapies served to alleviate PLP.

Risk Of Bias

The quality of the reports was evaluated using the risk of bias assessed using Cochrane Collaboration's tool for RCTs[9] and risk of bias in non-randomized studies of interventions (ROBINS-I) tool for PCS[10]. The risk of bias for each report was rated independently from low, moderate, serious, or critical by two authors, and any discrepancies were resolved by reciprocal discussion.

Statistical analysis

The meta-analysis was conducted using Review Manager (RevMan, v5.4 Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014). The mean difference (MD) was used on the original measurement scale to determine the magnitude of the impact on the VAS score. Pooled estimates of each outcome for each treatment were obtained via the DerSimonian and Laird method using a random-effects model[11]. Statistical significance threshold was accepted as $P<0.05$. The I^2 statistic was used to assess heterogeneity of trial results used to construct pooled estimates of effect[12].

RESULTS

A total of 15 studies, 8 in mirror therapy[6,8,13-18] (214 participants), and 7 in VR[7,19-24] (86 participants) totalling 300 participants met our inclusion criteria (Figure 1). Mean age ranged between 36.4 - 63 years (77% male), and 61% lower limb amputation. The number of treatment sessions ranged from 1- 56 for mirror therapy and 1- 20 for VR. The length of sessions treatment ranged from 5 - 25 minutes in mirror therapy, and 10 - 120 minutes in VR. All studies used VAS scores as outcome measure. Two studies used short-form McGill Pain Questionnaire (SF-MPQ) to describe different manifestations of pain, such as tingling and cramps, and patients ranked their use of each descriptor on a scale of 0 to 3.

Both mirror therapy and VR therapy led to a VAS reduction (Figures 2). The mean reduction in VAS scores of mirror therapy was 2.54 (95%CI 1.42-3.66; $P<0.001$) (Figure 2A), and VR was 2.24 (95%CI 1.28-3.20; $P<0.001$) (Figure 2B). The inter-study heterogeneity was high among mirror therapy (I^2 = 88%) but low among VR (I^2 = 45%). There was no statistically significant difference on the VAS scale in pain alleviation between mirror therapy and VR ($P=0.69$). There was no evidence of substantial inter-study heterogeneity (I^2 = 0%).

Sensitivity analysis was undertaken to determine whether there is a statistically significant difference between mirror therapy and VR compared to the control measures used in each study. The randomized controlled trials that used case- and control-intervention and pre- and post-intervention among mirror therapy are presented in Figures 3. Mean reductions of VAS scores in mirror therapy were 2.80 (95%CI 1.10-4.51; $P<0.001$) among case- and control-intervention (Figure 3A.1), and 0.91 (95%CI -2.28-4.10; $P=0.58$) among pre- and post-intervention (Figure 3A.2). There was evidence of substantial inter-study heterogeneity both in case- and control-intervention (I^2 = 88%) and in pre- and post-intervention (I^2 = 94%). There was no statistically significant difference on the VAS scale in pain alleviation between case- and control-intervention and pre- and post-intervention (*P*=0.31) and there was no evidence of substantial inter-study heterogeneity (I^2 = 4.8%).

The same pattern presents among VR therapy, mean reductions of VAS scores were 2.45 (95%CI 0.88-4.02; *P*=0.002) among case- and control-intervention (Figure 3B.1) and 1.72 (95%CI -1.20-4.63; *P*=0.25) among pre- and post-intervention (Figure 3B.2). The inter-study heterogeneity was low among case- and control-intervention (I^2 = 0%) but high among pre- and post-intervention (I^2 = 79%). There was not a statistically significant difference on the VAS scale in pain alleviation between case- and control-intervention and pre- and post-intervention (*P*=0.66). There was no evidence of substantial inter-study heterogeneity (I^2 = 0%).

Risk of bias for the mirror and VR therapy assessed by random sequence generation (Figure 4) showed a high risk in three studies since they were not double-blinded. Almost all studies used intention-to-treat analysis or did not have any dropouts, to minimize risk of incomplete outcome data. Most studies lacked information of selective reporting bias as they did not mention the study protocol.

DISCUSSION

In this meta-analysis and systematic review of data from over a three hundred patients with PLP, we show that mirror therapy and VR therapy significantly reduced pain. Both treatments have similar effect sizes, with more than doubling the likelihood of decreasing mean PLP levels.

The pain reduction observed in this analysis is consistent with the earlier but not all findings[25], although the latter mostly in children. All 6 studies in the mirror therapy group experienced a reduction in pain, and the median reduction in VAS was 2.4 which is very similar to the 2.54 average pain reduction in mirror therapy[3] patients in Figure 2. VAS is a universal and easy-to-use one-dimensional scale that has been adopted by many studies. In trauma patients, a difference of 1.3 in VAS represents the smallest measurable change in pain severity[26], which is clinically important and determines whether the patient is "a little more painful" or "a little less painful". However, Bird and Dixon[27] found that when the initial VAS score is lower than 3.4, a change of 1.3 represents a clinically significant change in pain. In addition, when the initial VAS score is at least 6.7, a change of 2.8 is required to represent a clinically significant change in pain. This implies that patients with more severe pain require greater changes in the VAS score to demonstrate clinically significant pain relief. The wide variation differences in VAS among patients still limit the use of VAS as a research tool for evaluating analgesic therapy.

Our meta-analysis and systematic review help to understand the effectiveness of mirror therapy and virtual reality in reducing PLP. Both treatments have very similar effect sizes in terms of the extent to which they cause a decrease in mean PLP levels. Therefore, this study emphasizes that both mirror therapy and virtual reality are equally feasible treatment options.

Our finding is important from a clinical and neurorehabilitation perspective. Many studies have emphasized that although most amputees benefit, some people actually experience increased pain and even other adverse reactions such as nausea and emotional distress after treatment[17]. Due to the small sample size and the number of studies, this study cannot explore many factors that can lead to inexplicable changes in patients' response to treatment. First, gender and amputation placement, female, and upper-limb amputees, have a greater propensity for PLP compared to male and lower-limb patients[28]. Second, the causes of amputation, such as trauma compared to vascular disease may cause one treatment to be more effective than another. Third, combination therapy where both interventions are used synergistically, and how they may interact with other treatment avenues such as pharmacological interventions. All of these factors have not been explored, and there is a clear lack of available literature. It is hoped that many well-designed and larger sample studies will be conducted, with the clear purpose of discovering the relationship between the effectiveness of these treatments and a variety of possible factors.

As in all studies, several limitations to our work need to be noted. We have not been able to assess effectiveness of therapy in different subgroups such as location or aetiology of the amputation. We have assessed only one therapy at a time. It is possible that using multiple therapeutic interventions simultaneously or in succession may improve outcome. Forest plots in this analysis revealed high inter-study heterogeneity which may be explained by a variation in study designs and patient characteristics. Interpreting the threshold of heterogeneity (I^2) can be misleading because the importance of inconsistency depends on several factors[12]. The importance of the observed value of I^2 depends firstly on the size and direction of the effect, and secondly on the strength of evidence from the chi-square test of the heterogeneity *P*-value, or the confidence interval of I^2 [29]. Some studies used mirror therapy but the mirror was covered so the reflection could not be used[13], whilst others utilised tactile stimuli applied to the stump[16], and another used TENS[8], this may introduce a risk of bias. There is therefore the possibility that our result may reflect a lack of standardised reporting. The numbers of participants vary between studies, while treatment duration ranges from five minutes to two hours which would contribute to significant inter-study heterogeneity. Finally, there was a low representation of female participants thus, the findings from this study should be interpreted cautiously in the female population.

CONCLUSIONS

Mirror therapy and VR are both equally efficacious in alleviating PLP, but neither is more effective than the other. However, due to small sample size and limited number of studies, factors such as gender, cause of amputation, site of limb loss or length of time from amputation, which may influence treatment success could not be explored.

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Legends

Figure 1: Flow chart of literature search.

Figure 2: Changes in VAS scores by mirror therapy and virtual reality therapy. SD, Standard Deviation; CI, Confidence Interval; df, degrees of freedom; *P*, probability.

Figure 3: Changes in VAS scores by mirror therapy and virtual reality therapy among case- and control-intervention and pre- and post-intervention. SD, Standard Deviation; CI, Confidence Interval; df, degrees of freedom; *P*, probability.

Figure 4: Risk of bias of RCTs evaluated Cochrane Collaboration's tool.