Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II (Protocol)

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[Intervention Protocol]

Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II

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ABSTRACT

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

To determine the effectiveness of physiotherapy interventions for treating pain and disability associated with CRPS types I and II.

BACKGROUND

Description of the condition

Complex regional pain syndrome (CRPS) is a persistent, painful and disabling condition that usually, but not exclusively, manifests in response to acute injury (e.g. fracture or crush injury) or surgery (Goebel 2011; Shipton 2009).

The diagnostic label 'CRPS' was introduced in the 1990s by the International Association for the Study of Pain (IASP) in order to standardise inconsistencies in terminology and diagnostic criteria (Merskey 1994). Two subcategories of CRPS were proposed: CRPS type I (formerly and variously referred to as reflex sympathetic dystrophy, algodystrophy, Sudek's atrophy) and CRPS type II (formerly referred to as causalgia, algoneurodystrophy), reflecting the absence or presence, respectively, of an associated nerve lesion (Coderre 2011; Todorova 2013).

CRPS is characterised by symptoms and signs typically confined to a body region or limb, but which may become more widespread (van Rijn 2011). The diagnostic criteria for CRPS originally proposed by the IASP (Merskey 1994) have since been revised in response to their low specificity and potential to overdiagnose cases of CRPS. The Budapest criteria proposed by Harden 2010 have enhanced diagnostic accuracy and are now widely accepted (Goebel 2011).The diagnosis of CRPS is clinical (Goebel 2011); cardinal features include: 1) continuing pain disproportionate to any inciting event; 2) the presence of clusters of various symptoms and signs reflecting sensory (e.g. hyperaesthesia, allodynia), vasomotor (e.g. asymmetries of temperature or skin colour, or both), sudomotor (e.g. oedema or altered sweating or both), motor (e.g. reduced range of motion, tremor) or trophic (e.g. altered hair or nails, or both) disturbances; and 3) the absence of any other medical diagnosis that might better account for an individual's symptoms and signs.

The pathophysiological mechanisms underlying CRPS are not fully understood (Harden 2010). Current understanding implicates multiple mechanisms including complex contributions from a maladaptive proinflammatory response and a disturbance in sympathetically mediated vasomotor control, together with maladaptive peripheral and central neuronal plasticity (Bruehl 2010; Marinus 2011; Parkitny 2013). Furthermore, mechanisms, and in consequence symptoms and signs, may vary between individuals and within individuals over the time course of the disorder, thus heightening the complexity (Marinus 2011).

The incidence of CRPS is not accurately known but population estimates indicate an incidence of somewhere between 5 and 26 cases per 100,000 person-years (Marinus 2011). A likely conservative 11-year period prevalence rate for CRPS of 20.57 per 100,000 people has been reported (Sandroni 2003). CRPS is three to four times more likely to occur in women than in men, and although it may occur at any time throughout the lifespan it tends to occur more frequently with increasing age (Shipton 2009). Genetic susceptibility may serve as an aetiological risk factor for the development of CRPS (de Rooij 2009). In individuals who develop CRPS after a fracture, intra-articular fracture, fracture-dislocation, pre-existing rheumatoid arthritis, pre-existing musculoskeletal comorbidities (e.g. low back pain, arthrosis) (Beerthuizen 2012) and limb immobilisation (Marinus 2011) may increase the risk of its development. Psychological traits, such as depression, anxiety, neuroticism and anger, have so far been discounted as risk factors for the development of CRPS (Beerthuizen 2009: Lohnberg 2013), although further prospective studies are required to substantiate this assertion (Harden 2013).

Individuals with CRPS are known to experience significant suffering and disability (Bruehl 2010; Lohnberg 2013). Preliminary data suggest that interference with activities of daily living, sleep, work and recreation is common and further contributes to a diminished quality of life (Galer 2000; Geertzen 1998; Kemler 2000; Sharma 2009).

Studies into the course of CRPS present contradictory findings. Whilst complete and partial symptom resolution within one year has been reported (Sandroni 2003; Zyluk 1998), other studies have indicated more protracted symptoms and impairments lasting from three to nine years (de Mos 2009; Geertzen 1998; Vaneker 2006). In addition, emerging evidence suggests that individuals with CRPS of an upper limb, which develops less often in response to a fracture, and whose affected limb is colder than the contralateral limb, may experience significantly longer disease duration than those with CRPS of a lower limb, which occurs more commonly after fracture, whose affected limb is warmer than the contralateral limb (de Mos 2009).

Although guidelines for the treatment of CRPS recommend an interdisciplinary multimodal approach, comprising pharmacological and interventional pain management strategies together with rehabilitation, psychological therapy and educational strategies (Goebel 2012; Harden 2013; Perez 2010; Stanton-Hicks 2002), determining the optimal approach to therapy remains clinically challenging (Cossins 2013; O'Connell 2013).

Description of the intervention

Guidelines recommend the inclusion of physiotherapy as part of the multimodal treatment of CRPS (Goebel 2012; Perez 2010; Stanton-Hicks 2002). Physiotherapy has been defined as "the treatment of disorders with physical agents and methods" (Anderson 2002) and for CRPS could include any of the following interventions employed either as stand-alone interventions or in combination: manual therapy (e.g. mobilisation, manipulation, massage, desensitisation); therapeutic exercise (including hydrotherapy); electrotherapy (e.g. transcutaneous electrical nerve stimulation (TENS); therapeutic ultrasound; interferential, shortwave diathermy; laser); physiotherapist-administered education (e.g. pain neuroscience education); as well as cortically directed sensory-motor rehabilitation strategies (e.g. graded motor imagery (GMI), mirror therapy, sensory motor retuning, tactile sensory discrimination training).

How the intervention might work

The precise mechanism(s) of action through which various physiotherapy interventions are purported to relieve the pain and disability associated with CRPS are not fully understood. Theories underpinning the use of manual therapies to relieve pain include the induction of peripheral or central nervous system-mediated analgesia, or both (Bialosky 2009; Goats 1994). Therapeutic exercise may induce analgesia, via endorphin-mediated inhibition (Nijs 2012), and improve function, and by extension disability, by restoring range of movement at affected joints and improving neuromuscular function (Kisner 2002). Theories underlying the use of electrotherapy modalities for pain relief variously include spinal cord-mediated electroanalgesia, heat- or cold-mediated analgesia and anti-inflammatory effects (Atamaz 2012; Robertson 2006). Pain neuroscience education may reduce pain and disability by helping individuals to better understand the biological processes underlying their pain in a way that positively changes pain perceptions and attitudes (Louw 2011). Other rehabilitation strategies, such GMI or mirror therapy, may provide pain relief or increase mobility, or both, by ameliorating maladaptive somatosensory and motor cortex reorganisation (Moseley 2005; Moseley 2012).

Why it is important to do this review

A number of systematic reviews suggest that physiotherapy interventions (e.g. exercise, GMI, TENS) employed in combination with medical management may be beneficial in reducing the pain and disability associated with CRPS (Daly 2009; Smith 2005). However, the inclusion of non-randomised clinical trials and case

series designs, together with the exclusion of studies involving individuals with CRPS type II as well as those published in a language other than English, may have biased these conclusions. Given the limitations of existing systematic reviews, together with the availability of potentially numerous physiotherapy treatment strategies for CRPS, an up-to-date systematic review of the evidence from randomised clinical trials for the effectiveness of these interventions may assist clinicians in their treatment choices and inform future clinical guidelines that may be of use to policymakers and those who commission health care for CRPS.

OBJECTIVES

To determine the effectiveness of physiotherapy interventions for treating pain and disability associated with CRPS types I and II.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials (including those of parallel, cluster-randomised and cross-over design) published in any language. Studies published in a language other than English will be translated. Studies in which participants were not randomised to intervention groups will be excluded.

Types of participants

Studies involving adults, aged 18 years or older, diagnosed with CRPS type I or II, or with an alternative diagnostic label for these conditions (e.g. reflex sympathetic dystrophy, causalgia), will be included. Trials will be grouped according to diagnosis (i.e. CRPS types I and II, or mixed). Since the use of formal diagnostic criteria for CRPS are inconsistent across studies (Reinders 2002), we will include studies using established or validated diagnostic criteria, including the Veldman criteria (Veldman 1993), IASP criteria (Merskey 1994), Budapest criteria (Harden 2010) and Atkins criteria (Atkins 2010), as well as studies that either predate these criteria or use non-standard diagnostic criteria.

Types of interventions

All randomised controlled comparisons of physiotherapy interventions, employed in either a stand-alone fashion or in combination, compared with placebo, no treatment or another intervention, or of varying physiotherapy interventions compared with each other, which are aimed at treating pain or disability, or both, associated with CRPS will be included. Studies in which such physiotherapy interventions, as defined in 'Description of the intervention', are delivered by non-physiotherapists (e.g. occupational therapists), will be included, and the professional discipline of the clinician delivering the intervention will be clearly reported.

Types of outcome measures

Primary outcomes

1. Changes in pain severity/intensity as measured using a visual analogue scale (VAS), numerical rating scale (NRS), verbal rating scale or Likert scale.
2. Changes in disability as measured by validated self-report questionnaires/scales or functional testing protocols.

Primary outcomes will be presented and analysed as change on a continuous scale or in a dichotomised format as the proportion of participants in each group who attained a predetermined threshold of improvement. For example, cut-points from which to interpret the likely clinical importance of (pooled) effect sizes will be judged according to provisional criteria proposed in the IMMPACT consensus statement (Dworkin 2008). Specifically, reductions in pain intensity compared with baseline will be judged as follows:

1. < 15% - 'no important change';
2. ≥15% - 'minimally important change';
3. ≥ 30% - 'moderately important change';
4. ≥ 50% - 'substantially important change'.

The cut-points for 'minimally', 'moderately' and 'substantially' important changes will be used to generate dichotomous outcomes, the effect size for which will be expressed as the risk ratio (or relative risk (RR)).

Secondary outcomes

The following secondary outcome measures will be analysed where such data is available:

1. changes in composite scores for CRPS symptoms;
2. changes in health-related quality of life using any validated tool;
3. changes in patient global impression of change (PGIC) scales;
4. incidence/nature of adverse effects.

Secondary outcomes will be similarly presented and analysed as change on a continuous scale or in a dichotomised format. For example, equivalent measures of treatment effect with respect to PGIC have been defined as; 'much' or 'very much' improved (moderate benefit) and 'very much' improved (substantial benefit) (Dworkin 2008).

Search methods for identification of studies

Electronic searches

The following electronic databases will be searched using a combination of controlled vocabulary, i.e. medical subject headings (MeSH) and free-text terms to identify published articles:

- Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*;
- MEDLINE (OVID);
- EMBASE (OVID);
- CINAHL (EBSCO);
- PsycINFO (OVID);
- LILACS;
- PEDro;
- Web of Science (ISI);
- SciVerse SCOPUS;
- Database of Abstracts of Reviews of Effects in *The Cochrane Library*;
- Health Technology Assessments.

The OVID MEDLINE search strategy is specified in Appendix 1. All database searches will be based on this strategy but adapted to individual databases as necessary.

Searching other resources

Reference lists

The reference lists of all eligible studies, key textbooks and previous systematic reviews will be searched in order to identify additional relevant studies. The list of included studies will be sent to content experts to help identify any additional relevant studies.

Unpublished data

In order to minimise the impact of publication bias the following registers and databases will be searched in order to identify unpublished research as well as research in progress:

- OpenGrey (System for Information on Grey Literature in Europe);
- Dissertation Abstracts (ProQuest);
- National Research Register Archive;
- Health Services Research Projects in Progress;
- Current Controlled Trials Register (incorporating the meta-register of controlled trials and the International Standard Randomised Controlled Trial Number);
- ClinicalTrials.gov;
- International Clinical Trials Registry Platform;
- Pan African Clinical Trials Registry;
- EU Clinical Trials Register.

Data collection and analysis

Selection of studies

The titles and abstracts of potential trials identified by the search strategy will be independently assessed by two review authors (KMS and BMW) for their eligibility. If the eligibility of a study is unclear from the title and abstract, the full paper will be assessed. Studies that do not match the inclusion criteria will be excluded (see section 'Criteria for considering studies for this review'). Disagreements between review authors regarding a study's inclusion will be resolved by discussion. A third reviewer (NEO) will assess relevant studies if resolution and agreement cannot be reached and a majority decision will be made. Studies will not be anonymised prior to assessment.

Data extraction and management

Two reviewers (KMS and BMW) will independently extract data from all included studies. Data will be extracted using a standardised form. Discrepancies and disagreements will be resolved by consensus. In cases where consensus cannot be achieved, the trial will be assessed by a third reviewer (NEO) for arbitration and a majority decision will be made. We will extract the following data from each study included in the review:

- country of origin;
- study design;
- study population (including diagnosis, diagnostic criteria used, symptom duration, age range, gender split);
- type of noxious initiating event: surgery, fracture, crush injury, projectile, stab injury or no event;
- type of tissue injured: nerve, soft tissue, bone;
- presence of medicolegal factors (that may influence the experience of pain and the outcomes of therapeutic interventions);
- concomitant treatments that may affect outcome: medication, procedures etc.;
- sample size - active and control/comparator groups;
- intervention(s) (including type, parameters (e.g. frequency, dose, duration), setting and professional discipline of the clinician delivering the therapy);
- type of placebo/comparator intervention;
- outcomes (primary and secondary) and time points assessed;
- adverse effects;
- author conflict of interest statements;
- assessment of risk of bias.

We will attempt to contact the authors of studies in the event that relevant data cannot be extracted from the published report.

Assessment of risk of bias in included studies

Risk of bias for each included study will be assessed using the Cochrane 'Risk of bias' assessment tool and classified as low, high or unclear, as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (Higgins 2011a). Design-specific (e.g. cluster randomised, cross-over study designs) risk of bias issues will also be considered (Higgins 2011b). Risk of bias in parallel study designs will be assessed according to the following criteria (using yes/no/unclear judgements): adequacy of sequence generation, allocation concealment, blinding of assessors, blinding of participants, blinding of therapists, assessment of incomplete outcome data and whether free of suggestions of selective outcome reporting or other sources of bias.

Risk of bias in cluster-randomised designs will be assessed (using yes/no/unclear judgements) according to the following criteria: adequacy of blinding of assessors, blinding of participants, blinding of therapists, whether free of suggestions of recruitment bias, whether baseline imbalances between randomised groups were assessed and accounted for, adequacy of assessment of incomplete outcome data, whether free from 'unit of analysis errors' and whether free of suggestions of selective outcome reporting or other sources of bias.

Risk of bias in cross-over designs will be assessed (using yes/no/unclear judgements) according to the following criteria: adequacy of sequence generation, blinding of assessors, blinding of participants, blinding of therapists, whether data are clearly free from carry-over effects, whether only first period data are available, adequacy of analysis (i.e. some form of paired analysis), adequate reporting of dropout rates between treatments and whether free of suggestions of selective outcome reporting or other sources of bias.

For all study types we will also assess the following criteria as recommended by Moore 2010:

- size (studies with < 50, 50 to 199, or 200 or more participants per arm will be rated as being at high, unclear or low risk of bias, respectively);
- duration of follow up (studies with a follow up of less than two weeks, two to seven weeks or eight weeks or more will be rated as being at high, unclear or low risk of bias, respectively).

Risk of bias assessment will be undertaken independently by two review authors (KMS and BMW). Disagreements will be resolved by discussion between the two review authors. If agreement cannot be reached, a third reviewer (NEO) will undertake a risk of bias assessment and a majority decision made.

Measures of treatment effect

Treatment effect sizes will be presented using appropriate metrics. RR with 95% confidence intervals will be calculated for dichotomised outcome measures.The number needed to treat to benefit (NNT) will be calculated as an absolute measure of treatment effect where possible.

The size of treatment effect on pain intensity, as measured with a VAS or NRS, will also be expressed using the mean difference (MD) (where all studies utilised the same measurement scale) or the standardised mean difference (SMD) (where studies used different scales). In order to aid interpretation of the pooled effect size the SMD will be back-transformed to a 0- to 100-mm VAS format on the basis of the mean standard deviation from trials using a 0 to 100 mm VAS where possible.

Unit of analysis issues

Estimates of treatment effect (and their standard errors (SE)) from cluster-randomised studies employing appropriate statistical analyses may be meta-analysed using the generic inverse-variance method in Review Manager (RevMan), as suggested in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (Higgins 2011b). Where such studies are judged to have employed inappropriate analyses, methods for 'approximately correct analysis' may be utilised where possible (Higgins 2011b).

Cross-over trials may be entered into a meta-analysis when it is clear that data are free from carry-over effects. We will combine the results of cross-over studies with those of parallel studies by imputing the post-treatment between-condition correlation coefficient from an included study that presents individual participant data and use this to calculate the SE of the SMD. These data may be entered into a meta-analysis using the generic inverse-variance method (Higgins 2011b).

Dealing with missing data

Where insufficient data are presented in the study report to enter into a meta-analysis, we will contact study authors to request access to the missing data.

Assessment of heterogeneity

We will attempt to deal with clinical heterogeneity by combining studies that examine similar conditions (e.g. CRPS types I and II, or mixed) or interventions (e.g. manual therapy, GMI). We will assess heterogeneity using the Chi^2 test to investigate the statistical significance of such heterogeneity, and the I^2 statistic to estimate the amount of heterogeneity. Where significant heterogeneity (P value < 0.1) is present, we will explore subgroup analyses. Preplanned comparisons are described in the section 'Subgroup analysis and investigation of heterogeneity'.

Assessment of reporting biases

We will consider the possible influence of publication/small study biases on review findings. Where possible, for studies that have

utilised dichotomised outcomes, we will test for the possible influence of publication bias on each outcome by estimating the number of participants in studies with zero effect required to change the NNT to an unacceptably high level (defined as an NNT of 10), as outlined by Moore 2008.

Data synthesis

Pooling of results will be performed where adequate data exist using Review Manager (RevMan 2012). Meta-analyses of outcome data will be undertaken only from suitably homogeneous studies using a random-effects model.

Where possible, extracted data will be grouped according to diagnosis (CRPS types I or II, or mixed), intervention, outcome (i.e. pain, disability) and duration of follow up (short-term: zero to less than two weeks postintervention; mid-term: two to seven weeks postintervention; and long-term: eight or more weeks postintervention). With regards to intervention, we will pool data from studies that investigated the same single therapy, separately for each therapy. We will pool studies of multimodal physiotherapy programmes together.

For all analyses, the outcome of the 'Risk of bias' assessments will be explicitly and clearly presented in the reporting. Where inadequate data are found to support statistical pooling, narrative synthesis of the evidence will be performed using the GRADE system (Guyatt 2008).

Subgroup analysis and investigation of heterogeneity

We plan to undertake subgroup analyses, where data allows, for:

- type of CRPS (I and II, or mixed);
- temporal characteristics of the disorder (i.e. acute (defined as symptoms and signs of CRPS of 0 to 12 weeks duration) and chronic (symptoms and signs of CRPS lasting $\geq$ 13 weeks).

Sensitivity analysis

Where sufficient data are available, we will conduct sensitivity analyses on risk of bias (investigating the influence of excluding studies classified at high risk of bias) and choice of meta-analysis model (investigating the influence of using a fixed-effect analysis).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Complex Regional Pain Syndromes/
2. "complex regional pain syndrome*".tw.
3. crps.tw.
4. (Post traumatic adj1 (algodystrophy or dystrophy or neurodystrophy or osteoporosis or pain syndrome)).tw.
5. "Minor causalgia".tw.
6. "Transient migratory osteoporosis".tw.
7. "Peripheral trophneurosis".tw.
8. "Sudeck's Osteodystrophy".tw.
9. "Neurovascular dystrophy".tw.
10. ((Major or mitchell*) adj1 causalgia).tw.
11. Sympathalgia.tw.
12. Chronic traumatic oedema.tw.
13. Sympathetic dystrophy syndrome.tw.
14. or/1-13
15. exp Physical Therapy Modalities/
16. physiotherap*.tw.
17. "physical therap*".tw.
18. manual therapy.tw.
19. manipulative therapy.tw.
20. ((therapeutic or therapy) adj2 exercise).tw.
21. exp Electric Stimulation Therapy/
22. (electrotherapy or TENS or "transcutaneous electrical nerve stimulation" or "therapeutic ultrasound" or interferential or "shortwave diathermy" or "laser therapy " or "heat therapy" or cryotherapy).tw.
23. graded motor imagery.tw.
24. mirror therapy.tw.
25. exp Musculoskeletal Manipulations/
26. tactile sensory discriminatory training.tw.
27. sensory-motor integration.tw.
28. sensory-motor re-tuning.tw.
29. hydrotherapy.tw.
30. (pain adj3 (advice or education)).tw.
31. (manipulation or massage or de-sensiti#ation or mobili#ation).tw.
32. or/15-31
33. 14 and 32
34. randomized controlled trial.pt.
35. controlled clinical trial.pt.
36. randomized.ab.
37. placebo.ab.
38. drug therapy.fs.
39. randomly.ab.
40. trial.ab.
41. or/34-40
42. exp animals/ not humans.sh.
43. 41 not 42
44. 33 and 43

CONTRIBUTIONS OF AUTHORS

KMS has conceived and designed the review protocol, will implement the search strategy, apply eligibility criteria, assess studies, extract and analyse data, and lead the write-up and updating of the review.

BW has informed the protocol design, will apply eligibility criteria, assess studies, extract and analyse data, and assist the write-up and updating of the review.

NOC has informed the protocol design, will act as the third reviewer, oversee the data synthesis, and assist the write-up and updating of the review.

DECLARATIONS OF INTEREST

All authors are qualified physiotherapists, though none currently practice in private health care or for a 'for profit' organisation.

KMS has received honoraria from Pfizer (Ireland) to speak at public events.

BW and NOC have no known conflicts of interest.