Additional exercise therapy for the recovery of function after stroke (Protocol)

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Additional exercise therapy for the recovery of function after stroke

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ABSTRACT

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

To assess whether additional exercise therapy has an impact on recovery following stroke when compared with routine exercise therapy.

The specific objectives of this review are twofold:

1. To examine the impact of additional exercise therapy time on functional recovery following stroke by reviewing RCTs that assess the effects of additional exercise therapy when compared with routine exercise therapy.

2. To determine a minimum threshold of additional exercise therapy time provided to the experimental group below which no clinically relevant benefit is observed.

BACKGROUND

Stroke is a significant cause of death and disability in every society in which it has been studied. It is both a preventable and a treatable disease. However, as public health, medical and social advances continue to extend life expectancy, the prevalence of stroke is likely to increase in the future (Braun 2007). Advances in neuroscience and clinical research have demonstrated that the human brain is capable of significant recovery after stroke provided that the correct treatment and stimuli are applied in adequate amounts and at the right time (Teasell 2004; Ward 2005). One major component of stroke rehabilitation is exercise therapy to minimise the effects of the brain cell damage and optimise re-learning. It is well recognised that for cortical re-organisation to occur after stroke, high levels of repetition of tasks and exercises that are both challenging and engaging are required (Kwakkel 2006; Plautz 2000; Pomeroy 2000).

The most common and widely recognised impairment following stroke is motor impairment, and much of the focus of stroke re-
habilitation is on the recovery of impaired movements and related functions. In the rehabilitation context, both physiotherapists and occupational therapists have traditionally been the mediators of motor recovery following stroke. Nonetheless, it has been suggested that the duration of exercise therapy that is delivered after stroke is, at best, homeopathic, and uncertainties still remain about the most appropriate level of therapy input (Kwakkel 2004; Pomeroy 2002). In the past few years, randomised controlled trials (RCTs) have examined the provision of additional or augmented exercise training by physiotherapists and occupational therapists. The results of these trials are inconsistent, and differences exist between the studies in terms of methodological quality, patient subgroups selected, frequency and intensity, timing and type of treatment in experimental and control groups, and outcome measures used to capture change. A recent overview of the available evidence on interventions for motor recovery after stroke suggests that, although the existing evidence is limited by poor trial designs, some interventions show promise for improving motor recovery, particularly those that have focused on high-intensity and repetitive task-specific practice (Langhorne 2009). These findings were supported by a systematic review that concluded that repetitive, task-specific training for lower limbs can result in functional gain after stroke when compared with other forms of usual care or attention control (French 2009). However, the authors suggest that further research is needed to explore the impact of the type and amount of task training for lower limb function, and how to maintain functional gain (French 2009). Therefore, the aim of this systematic review and meta-analysis is to examine the effects of augmented treatment time by reviewing studies that assess the effects of additional exercise therapy when compared with routine exercise therapy on functional recovery following stroke. For this review, we define exercise therapy as ‘a regimen or plan of physical activities designed and prescribed for specific therapeutic goals’ (MEDLINE MeSH term).

Description of the condition

The specific impairments observed after stroke depend on the area of the brain affected. Recovery is related to the site, extent and nature of the lesion, the integrity of the collateral circulation and the premorbid status of the individual (Baer 2004). The most common physical consequence after stroke is hemiplegia or hemiparesis, which results in weakness of the muscles of the arm, leg, trunk and sometimes face on one side of the body. Other sequelae of stroke include cognitive, sensory, communication and perceptual impairments. Rehabilitation aims to enable people with such impairments and activity limitations to reach and maintain optimal functioning in the physical, intellectual, psychological and social domains (WHO 2010). Exercise therapy is a cornerstone of rehabilitation, and it is well recognised that exercise therapy has a positive impact on motor recovery following stroke.

Description of the intervention

Many different treatment approaches are available for people with motor impairments after stroke. This review will consider any intervention that is exercise based and is designed to deliver additional or augmented time in exercise therapy to the intervention group when compared with the control group. However, we will not include studies in the review that consider a massed practice approach such as the effectiveness of constraint-induced movement therapy or application of special equipment to augment therapy. We will review studies that examine the efficacy of repetitive task training where the aim of the study is to increase the duration of exercise therapy or the amount of time that the patient spends exercising. Therefore, there needs to be a clear treatment difference between the two groups. For this review, we define treatment difference as the amount of time spent on exercise therapy in the experimental group minus the amount of time spent in the control group.

How the intervention might work

Advances in neurophysiological research support the dynamic characteristics of the brain to re-organise after injury (Dobkin 2005; Nudo 1996; Nudo 2001; Plautz 2000). This evidence has enabled researchers and clinicians to design and test interventions that influence cerebral adaptations following stroke by preventing further neuronal degeneration and activating new neuronal pathways. Cortical re-organisation can be enhanced after stroke by completing high levels of repetition of tasks and exercises that are both challenging and engaging (Kwakkel 2006; Plautz 2000; Pomeroy 2000). However, while we know that exercise-based therapy enhances motor recovery after stroke, we do not know the most appropriate amount of exercise therapy. Therefore, this review sets out to examine whether additional exercise therapy has an impact on functional recovery following stroke and, furthermore, to determine whether there is a minimum threshold of additional exercise therapy time that needs to be provided to the experimental group below which no clinically relevant benefits are observed.

Why it is important to do this review

In contrast with coronary heart disease and cancer, the burden of stroke lies with long-term disability as opposed to death. Therefore, any rehabilitation intervention that can speed up recovery and reduce long-term disability will have a major impact on the individual and the social burden of the illness. In view of the limited resources available to provide additional therapy, the purpose of this systematic review is to determine the strength of current evidence for providing additional exercise therapy following stroke. This review may serve to guide clinicians in determining the optimal amount of exercise therapy that is required for functional recovery following stroke. Furthermore, as most patients with stroke
survive the initial injury, the most profound effect on patients and families is usually through long-term impairment, limitation of activities, and reduced participation. This systematic review serves to examine the effects of additional treatment time when compared with routine treatment time on functional recovery following stroke.

**OBJECTIVES**

To assess whether additional exercise therapy has an impact on recovery following stroke when compared with routine exercise therapy.

The specific objectives of this review are twofold:

1. To examine the impact of additional exercise therapy time on functional recovery following stroke by reviewing RCTs that assess the effects of additional exercise therapy when compared with routine exercise therapy.

2. To determine a minimum threshold of additional exercise therapy time provided to the experimental group below which no clinically relevant benefit is observed.

**METHODS**

Criteria for considering studies for this review

**Types of studies**

We propose to include only RCTs comparing additional exercise therapy with routine therapy. We will not include studies that investigate the effectiveness of constraint-induced movement therapy or use of special equipment to augment exercise therapy, such as balance platforms, treadmill training, biofeedback equipment or robotic therapy. We will include trials with or without blinding of the participants, therapists or assessors.

**Types of participants**

We will include adults aged 18 years and over, male and female, with a definition of stroke as defined by the World Health Organization (Hatano 1976), where additional exercise therapy is provided to one of the treatment groups.

**Types of interventions**

Interventions of interest are those where ‘additional’, ‘augmented’ or ‘increased duration’ of exercise therapy is compared with ‘normal’, ‘routine’ or ‘traditional’ levels of exercise therapy. We define exercise therapy as ‘a regimen or plan of physical activities designed and prescribed for specific therapeutic goals’ (MEDLINE MeSH term) intended to restore optimal functioning, and we will include both occupational and physical therapy interventions for this review. There is a general lack of consensus on what constitutes traditional or routine exercise therapy, and the exact definition can only be considered in relation to each individual study: in many cases this definition is not provided. However, we will only include studies where the control group in the study receives some form of exercise therapy. We will exclude studies if the routine exercise therapy delivered to the two groups is not comparable. Additional, augmented or increased duration of exercise therapy refers to the amount, in minutes, of exercise therapy that people with stroke received that is in excess of their routine exercise intervention. The review will examine the effects of increased duration of exercise therapy on upper and lower limb impairment and function, general function, gait and balance, and will include both hospital- and community-based programmes. If no exercise therapy is delivered to the control group, then we will not include such studies. ‘Frequency’ refers to the number of days of exercise per week of exercise delivery. We will also include studies that examine the value of increasing the frequency of exercise therapy.

**Types of outcome measures**

We will examine outcome measures that may be classified using the International Classification of Functioning, Disability and Health. We will focus on outcomes that map onto structural impairment and limitation of activity or participation (WHO 2010). The outcome measures described do not constitute an exhaustive list and will not form part of the inclusion criteria for the review.

**Primary outcomes**

Functional ability in activities of daily living. We will include studies using the following validated scales: Barthel Index, Functional Independence Measure, Modified Rankin Scale and Katz Index of Independence in Activities of Daily Living.

**Secondary outcomes**

- Measures of upper and lower limb impairment, including the Fugl-Meyer Assessment upper limb and lower limb sections, Motricity Index, and clinical or biomechanical, or both, measurements of muscle strength.
- Measures of activity, including the Motor Assessment Scale or modified version, Berg Balance Scale, Action Research Arm Test, Frenchay Arm Test, measures of gait speed (Timed Up and
Go test, timed walk tests, walking speed) and other standardised activity measures.
- Measures of participation in extended activities of daily living, such as Nottingham Extended Activities of Daily Living scale, Frenchay Activities Index, Reintegration to Normal Living Index and General Health Questionnaire.
- Length of hospital stay.
- Adverse events including falls.

Search methods for identification of studies
See the 'Specialized register' section in the Cochrane Stroke Group module. We will search for relevant trials in all languages and arrange translation of trial reports published in languages other than English.

Electronic searches
We will search the Cochrane Stroke Group Trials Register and the following health-related, subject-specific and electronic bibliographic databases:
- The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, latest issue);
- MEDLINE (1950 to present) (Appendix 1);
- EMBASE (1980 to present);
- CINAHL (1982 to present);
- AMED (Allied and Complementary Medicine Database) (1985 to present);
- PEDro (Physiotherapy Evidence Database) (http://www.pedro.org.au);
- CIRRIE Database of International Rehabilitation Research (http://cirrie.buffalo.edu/search/index.php);
- The Cochrane Database of Systematic Reviews (The Cochrane Library, latest issue);
- Database of Abstracts of Reviews of Effects (DARE) (The Cochrane Library, latest issue);
- Electronic dissertation/theses databases: ProQuest Dissertations & Theses Database (PQDT);
- OT Search (http://www1.aota.org/otsearch);
- O'Tseeker (http://www.otseeker.com);
- REHABDATA Database (http://www.naric.com/research/rehab);
- SPORTDiscus (http://www.ebscohost.com/public/sportdiscus);
- ClinicalTrials.gov (http://clinicaltrials.gov);
- Current Controlled Trials (www.controlled-trials.com);
- Trials Central (www.trialcentral.org);
- Stroke Trials Registry (www.strokecenter.org/trials);

Searching other resources
To identify further published, unpublished and ongoing trials, we will:
- handsearch the reference lists of included trials and review articles about additional exercise therapy after stroke;
- track citations using Web of Science Cited Reference Search for all included studies;
- contact experts active in this field (including authors of included trials and excluded studies identified as possible preliminary or pilot work).

Data collection and analysis
One review author will run all the electronic searches, download references into bibliographic software and remove duplicates. One review author will exclude all titles that are clearly not relevant to the nature of the topic (stroke and exercise therapy) and clearly not RCTs. We will rigorously conduct this process and will file all articles deemed ineligible for inclusion separately. We will obtain the full abstracts for the remaining titles that concern stroke and exercise therapy. Two review authors will independently consider each of these abstracts, excluding studies that do not fulfil the inclusion criteria. The review authors will meet to resolve any disagreements through discussion. We will obtain the full text of papers for all studies remaining at this stage.

Selection of studies
Two review authors will independently apply the selection criteria, considering and documenting the type of studies, type of participants, intervention, comparison intervention and outcome measures. Each review author will finally classify each study as 'include' or 'exclude'. If there is disagreement between these two reviewers, they will reach consensus through discussions involving a third review author. We will document excluded studies in the 'Characteristics of excluded studies' table and will provide a reason for exclusion. We will not list studies that we excluded because they include participants who did not receive additional exercise therapy following stroke in the 'Characteristics of excluded studies' table unless the two review authors agree that there is a clear reason to do so.

Data extraction and management
We will use a pre-designed data extraction form to extract data from the included studies. Two review authors will independently document the following.
- Participants: number of participants, age, gender, baseline functional status or level of impairment.
- Methods: inclusion criteria, time since stroke, and type, nature and location of lesion. We will document the method of diagnosing stroke.
Interventions: description of interventions given to each treatment group including the duration, type and frequency. We will document the background of the person providing the intervention (e.g. occupational therapist, physiotherapist, physiotherapy/occupational therapy assistant, family).

Outcomes: we will document the primary and secondary outcomes relevant to this review. If a study has used different methods of measuring the same outcome, we will note the outcome to be used for any subsequent analysis.

We will note any important confounding variables. If more than two intervention groups are included in the study, we will note the method of including these groups in any subsequent analysis. The two review authors will resolve any data extraction discrepancies through discussion. If disagreement persists, a third author will independently extract the data.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias of each included study against key criteria: random sequence generation; allocation concealment; blinding of participants, personnel and outcomes; incomplete outcome data; selective outcome reporting; and other sources of bias (such as whether groups were similar at baseline, the intervention was inappropriately administered or subgroups were selectively reported) in accordance with the methods recommended by The Cochrane Collaboration (Higgins 2011). We will explicitly judge each of these criteria using low risk of bias, high risk of bias or unclear risk of bias (either lack of information or uncertainty over the potential for bias). We will resolve disagreements by consensus and consult a third review author to resolve disagreements if necessary. We will produce a 'Risk of bias' table, graph and summary figure to illustrate the potential biases within each of the included studies.

Measures of treatment effect

We will use the Cochrane Review Manager software (RevMan) to carry out statistical analyses to determine the treatment effect. For dichotomous variables we will calculate the treatment effect using a fixed-effect or random-effects model and report it as odds ratios (OR) with 95% confidence intervals (CI). For continuous data we will calculate the treatment effect using standardised mean differences (SMD) and 95% CI where different studies used different scales to assess the same outcome, and calculate mean differences (MD) and 95% CI where studies have all used the same method of measuring outcome.

Unit of analysis issues

The primary outcome of functional ability in activities of daily living and secondary outcomes of levels of impairment, activity, balance, gait parameters and functional ability in extended activities of daily living comprise either ordinal data from measurement scales or continuous data, and we will analyse these as continuous variables. Where reported outcomes have a scale where a lower value indicates a better outcome (e.g. number of falls) we will multiply the reported values by −1 so that in all analyses a higher value will indicate a better outcome. If studies report change values and the baseline value is available, we will calculate the value at follow-up (change value — baseline value). If studies report change values and the baseline value is not available, we will use these data in meta-analyses but plan sensitivity analyses to investigate the effect of including these data. We will analyse adverse events and death as dichotomous variables.

Dealing with missing data

If an included study does not report a particular outcome but it has been included in the battery of measures administered, we will contact the authors for the original data. If we are unsuccessful in obtaining the data, we will not include that study in the analyses of that outcome.

If an included study has missing data (e.g. reports means but not standard deviations for the follow-up data) we will contact the authors for the missing data. If we are unsuccessful, then we will take logical steps to enter an assumed value. Such steps may include estimating a standard deviation based on a reported standard error, estimating a follow-up standard deviation based on a baseline value, using the median as a proxy for the mean, and using and a multiple of 0.75 times the interquartile range or 0.25 times the range as a proxy for the standard deviation values (Hozo 2005). We plan to do sensitivity analyses to investigate the effect of entering assumed values.

Assessment of heterogeneity

We will determine heterogeneity using visual inspection of the forest plots and the Chi² and I² statistics. We will consider I² greater than 50% as substantial heterogeneity. If I² is less than or equal to 50% we will used a fixed-effect meta-analysis. If I² is greater than 50%, we will explore the individual trial characteristics to identify potential sources of heterogeneity, using pre-planned subgroup analyses. Where there is substantial heterogeneity we will perform a meta-analysis using both fixed-effect and random-effects modelling to assess sensitivity to the choice of modelling approach. If we find non-identical results we will report the most conservative outcome.

Assessment of reporting biases

We will attempt to avoid reporting biases by using a comprehensive search strategy that includes searching for unpublished studies and searching trials registers.
Data synthesis
Two review authors will independently extract data from the included trials. One review author will enter the data into RevMan, and the other review author will check the entries. They will resolve any disagreements through discussion, with reference to the original report.

Subgroup analysis and investigation of heterogeneity
We intend to explore heterogeneity by additional subgroup analyses to investigate the effect of:
- time since stroke;
- duration of additional intervention;
- difference between the control group and the intervention group in terms of amount of therapy provided to the control group as a fraction of the intervention group;
- type of intervention (upper limb therapy only; lower limb therapy only, upper and lower limb therapy, balance exercise only);
- level of impairment at baseline;
- compliance with additional intervention.

Sensitivity analysis
We intend to carry out a sensitivity analysis (if necessary) to explore the effect of the following methodological features.
- Allocation concealment: we will re-analyse data, excluding trials with inadequate or unclear allocation concealment.
- Masking of outcome assessor: we will re-analyse data, excluding trials without or with unclear masking of outcome assessor.
- Missing outcome data: we will re-analyse the data, excluding trials with inadequate or unclear methods of dealing with missing outcome data.

References

Additional references
Baer 2004

Braun 2007
Braun SM, Beurskens AJ, Van Kroonenburgh SM, Demarteau J, Schols JM, Wade DT. Effects of mental practice embedded in daily therapy compared to therapy as usual in adult stroke patients in Dutch nursing homes: design of a randomized controlled trial. BMC Neurology 2007;7:34.

Dobkin 2005

French 2009

Hatano 1976

Higgins 2011

Hozo 2005

Kwakkel 2004

Kwakkel 2006

Langhorne 2009

Nudo 1996

Nudo 2001

Plautz 2000
Appendix 1. MEDLINE search strategy
We will use the following strategy, which uses a combination of controlled vocabulary (MeSH) and free-text terms, for MEDLINE and will modify it, as appropriate, to suit other databases.
1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or brain ischemia/ or carotid artery diseases/ or cerebrovascular accident/ or brain infarction/ or cerebrovascular trauma/ or hypoxia-ischemia, brain/ or intracranial arterial diseases/ or intracranial arteriovenous malformations/ or intracranial hemorrhages/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cva or cerebral vascular or cerebrovascular)
3. (brain or cerebrum or cerebellum or intracranial or intracerebral)
4. (ischemia or infarct or thrombosis or emboli or occlusion)
5. 1 or 2 or 3 or 4
6. physiotherapy or "physical therapy" or "occupational therapy"
7. exercise or "exercise therapy" or "exercise movement techniques"
8. 6 and 7
9. 5 and 8
10. (upper extremity) or (upper limb)
11. (arm or shoulder or elbow or forearm or hand or wrist or finger or fingers)
12. 10 or 11
13. (Lower Extremity) or (lower limb)
14. (leg or hip or knee or ankle or toe or toes)
15. 13 or 14
16. rehabilitation/ or "recovery of function" or "motor recovery"
17. 9 and 12
18. 9 and 15
19. 9 and 16
20. 17 and 18 and 19
21. intensity or frequency or duration or "dose-response relationship"
22. 20 and 21
23. limit 22 to humans

Pomeroy 2000

Pomeroy 2002

RevMan 2011

Teasell 2004

Ward 2005

WHO 2010

* Indicates the major publication for the study
HISTORY


CONTRIBUTIONS OF AUTHORS

Rose Galvin will lead this review, run the searches, identify the relevant articles, act as a review author and write the drafts of the review.

Sheila Lennon will provide methodological and content expertise, assist with the data extraction, and read and comment on the final drafts.

Tara Cusack will assist with the data extraction and review the methodological quality of the studies, as well as reading and commenting on the final drafts.

Brendan T Murphy will carry out all the analyses on the extracted data, as well as commenting on the final drafts of the review.

Frances Horgan will provide methodological and content expertise and act as a second reviewer, as well as reading and commenting on the final drafts.

Emma Stokes will act as an additional reviewer where there is uncertainty and provide content and methodological expertise, as well as reading and commenting on the final drafts of the review.

DECLARATIONS OF INTEREST

None known.