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Rehabilitation of cognitive deficits poststroke: protocol for a systematic review and meta-analysis of randomised controlled trials of non-pharmacological interventions

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ABSTRACT

Introduction Stroke is among the leading causes of death and disability worldwide. Poststroke cognitive impairment is a common sequela of stroke. The burden of cognitive impairment poststroke has significant impacts on the individual poststroke, their family and wider society. Despite the prevalence and associated burden of poststroke cognitive impairment, the optimal approach to rehabilitate cognitive deficits poststroke has yet to be established. A range of conservative interventions for cognitive impairment poststroke exist including self-efficacy training, physical activity interventions, neuropsychological interventions, electronic interventions, music therapy and occupational therapies. This systematic review aims to explore the totality of evidence with regard to non-pharmacological rehabilitation interventions wherein the primary or secondary aim is to improve cognitive function in individuals poststroke.

Methods and analysis A systematic review of randomised controlled trials which investigate the effectiveness of interventions wherein the primary or secondary aim is to improve cognitive function in individuals poststroke will be conducted (August 2019). The following electronic databases will be searched: PubMed, Embase, CINAHL, CENTRAL and PsycInfo. Reference lists of all identified studies will be reviewed to identify additional studies for inclusion. Titles and abstracts will be screened independently by two review authors for inclusion and exclusion. Any disagreement regarding inclusion will be resolved by discussion or by referral to a third assessor if necessary. Methodological quality will be assessed using the Cochrane Risk of Bias Tool for Randomised Controlled Trials. Meta-analyses will be performed if studies are sufficiently homogeneous. The review will be reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Ethics and dissemination As this systematic review will collect secondary data only, ethical approval is not required. Findings will be disseminated through presentations and peer-reviewed journals.

Trial registration number CRD42019125289.

Strengths and limitations of this study

- This is the first systematic review to synthesise the totality of evidence regarding non-pharmacological rehabilitation interventions which improve cognitive deficits post-stroke.
- Robust and transparent methods used to identify, select, appraise and synthesise findings.
- Reporting in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.
- Methodological quality assessed using Cochrane Risk of Bias tool.
- Pharmacological interventions to address cognition poststroke will not be included.

INTRODUCTION

Stroke is among the leading causes of disability worldwide.[1] The prevalence of stroke survivors is projected to increase given advancements in acute stroke care services in conjunction with an ageing world population.[2] Given the increased prevalence of individuals surviving a stroke, coupled with an increase in the number of disability-adjusted life-years, stroke rehabilitation and the prevention of stroke-related residual disability have become increasingly important. Cognitive impairment is a common clinical feature of stroke reported in 56.6% of ischaemic stroke survivors at 6 months poststroke.[3] The presence of cognitive impairment poststroke is independently associated with lower quality of life at 12 months poststroke,[4] higher levels of death and institutionalisation,[5] increased carer burden[6] and increased healthcare costs.[7]

A collaboration of stroke survivors, carers and healthcare professionals within the James Lind Alliance (UK) identified that optimum

approaches to improve cognitive impairment poststroke were among the top 10 research priorities with regard to life after stroke.[8] This finding is also supported by the Intercollegiate Stroke Working Party national clinical guidelines for stroke where it is acknowledged that although there have been developments within stroke rehabilitation literature; significant gaps exist in relation to cognition after stroke.[9] Furthermore, a meta-summary of qualitative studies regarding stroke survivors' experiences of rehabilitation found that individuals with stroke report an emphasis placed on the rehabilitation of physical deficits with a neglect towards non-physical needs such as social re-integration and psychological support poststroke.[10]

As illustrated by the diversity and range of neuropsychological assessments, cognition is not a unitary concept.[11] Cognitive impairment poststroke encompasses a variety of deficits across multiple domains and typically includes memory, attention, executive function, language and visuoperceptual ability.[12] Various cognitive domains enable complex mental processes to occur which allow an individual to select and process information within their environment.[13] Given the complex nature of cognitive functioning, a broad range of interventions exist to improve cognitive function in individuals poststroke. Such interventions include, but are not restricted to, music therapy, resistance exercise training, aerobic exercise training, repetitive transcranial magnetic stimulation, occupational therapies, neuropsychological interventions, cognitive strategy training, self-efficacy training, virtual reality training, cognitive computerised training and electroacupuncture interventions.[14] Much of the previous research in this area has examined specific cognitive rehabilitation interventions on single domains of cognition poststroke. Six Cochrane reviews have explored the effectiveness of specific cognitive rehabilitation interventions on specific domains of cognitive function poststroke.[15–20] Cognitive rehabilitation is defined as 'a systematic functionally orientated intervention of therapeutic cognitive activities based on the assessment and understanding of the patient's brain behaviour deficits'.[13] There is a need to capture a broader range of interventions other than specific cognitive rehabilitation interventions with regard to improving cognitive function poststroke. Moreover, the effectiveness of interventions across multiple domains of cognitive function needs to be investigated, given the diffuse nature of cognitive impairment poststroke.[21] Studies focusing on the rehabilitation of single cognitive domains fail to capture the interrelated and highly overlapping nature of cognitive domains.[11]

In consideration of the effect of interventions other than specific cognitive rehabilitation interventions on cognitive impairment poststroke, 'cognitive rehabilitation' is arguably too narrow a term to use regarding the remediation cognitive impairment poststroke. Rather, there should be a focus on the broader picture of the rehabilitation of cognitive deficits poststroke. The efficacy of all types of non-pharmacological rehabilitation interventions on cognitive deficits poststroke needs to be investigated. The breadth of interventions identified will capture the totality of evidence with regard to all types of non-pharmacological rehabilitation interventions to rehabilitate cognitive deficits in individuals poststroke. Furthermore, given the diffuse nature of cognitive deficits poststroke, there is a need to investigate the effects of interventions across all domains of cognition poststroke as opposed to focusing on domain-specific cognitive deficits.

In contrast with previous literature which has focused on specific single-domain cognitive rehabilitation interventions, this review will include all forms of non-pharmacological rehabilitation interventions wherein the primary or secondary aim is to improve cognitive function poststroke. Randomised controlled trials of interventions wherein the primary or secondary aim is to improve cognitive function in individuals poststroke will be evaluated. In the context of this review, cognition will include general cognitive function as assessed by a standardised cognitive screening assessment. The review will also capture deficits across the domains of attention, memory, executive function, perception, limb apraxia and neglect as outlined in the latest Australian Clinical Guidelines for Stroke (2017). To this end, this review aims to examine the totality of evidence with regard to non-pharmacological rehabilitation interventions wherein the primary or secondary aim is to improve cognitive function in individuals poststroke.

METHODS

Study design

The current systematic review protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[22] In accordance with the PRISMA-P guidelines, this protocol was registered with the International Prospective Register of Systematic Reviews on 13 February 2019.

Eligibility criteria

Types of study

Randomised controlled trials and quasi-randomised control trials will be included, as defined by the Cochrane Handbook for Systematic Reviews of Interventions.[23] The precrossover component of randomised and quasi-randomised crossover trials will also be included, as will cluster trials. Studies published in the English language with full text available will be included.

Participants

Adults aged 18 years or older with a clinical diagnosis of ischaemic or haemorrhagic stroke are eligible for inclusion. Individuals with a confirmed cognitive impairment poststroke as specified by the authors within each trial will be included. Individuals may be in the acute, subacute or chronic stage poststroke.

Mixed aetiology studies (eg, traumatic brain injury and stroke mix) will be included if separate data are reported on individuals with stroke which can be clearly extracted for review. Participants post-transient ischaemic attack will be excluded, as will patients with dementia and patients with delirium. Individuals with cognitive impairment diagnosed before stroke onset will also be excluded.

Interventions

Interventions of which the primary or secondary aim is to improve cognitive function after stroke will be included. Interventions may focus on general cognitive function as assessed by a standardised cognitive screening assessment such as Mini-Mental State Examination (MMSE) score, Montreal Cognitive Assessment scale (MoCA) score, the Addenbrooke Cognitive Examination (ACE). Interventions may also focus on cognitive in relation to the following cognitive domains: executive function, attention, memory, perception, limb apraxia and neglect as outlined in the Australian Clinical Guidelines for Stroke Management (2017).

Interventions may be of any type or duration or time since stroke. Some anticipated interventions may include, but are not restricted to:

- Neuropsychological interventions.
- Exercise interventions: aerobic training, resistance training, flexibility training, balance training, Tai Chi.
- Electronic interventions, for example, use of iPads, mobile phone apps.
- Self-efficacy training.
- Patient education interventions.
- Cognitive rehabilitation interventions.
- Virtual reality training.
- Cognitive computerised training.
- Acupuncture/electroacupuncture interventions.
- Non-invasive brain stimulation.

Controls

Eligible control groups include:

Passive controls

- Usual/standard care control.
- No treatment control.
- Wait-list control.

Active controls

- Comparing different forms of interventions which are hypothesised to mediate improvements in cognitive function poststroke.

Outcomes

The primary outcome is change in cognitive function post intervention in individuals with poststroke cognitive impairment. Outcome measures may focus on a domain-specific aspect of cognition such as executive function, attention, memory, perception, limb apraxia and neglect as outlined in the Australian Clinical Guidelines for Stroke Management (2017). Outcome measures may also cover a range of different cognitive functions in a single measure or give a measure of general cognitive status also.

Secondary outcome measures include quality of life, functional abilities, physical fitness, mobility, mood, participation and return to work.

Anticipated outcome measures include, but are not restricted to:

- Standardised tests or cognitive screening tools which provide a general cognitive function score, for example, MMSE, MOCA, ACE.
- Subjective cognitive function, for example, cognitive failures questionnaire.
- Neuropsychological test batteries.
- Performance tests, for example, the Trail-Making Test, the Clock Drawing Test.
- Functional assessments, for example, personal/domestic Activities of Daily Living, community-based tasks, assessment of motor and process skills, functional independence measure or functional assessment measure.

Pharmacological interventions (including over-the-counter medications) will be excluded.

Public and patient involvement

No patient involved.

Search

The following electronic databases will be searched: PubMed, Embase, CENTRAL, PsycInfo and CINAHL (August 2019). The search strategy was developed in consultation with an academic librarian (LD, University of Limerick). The search strategy includes search terms relating to the population of interest (individuals post-stroke), the intervention (breadth of rehabilitation interventions as described), study type (randomised controlled trials) and the primary outcome of interest (change in cognitive function poststroke). To illustrate, the full electronic database search string for the CINAHL database is detailed in online supplementary appendix 1.

Reference lists of included studies will be searched to identify potentially eligible studies and authors of key texts may be contacted as appropriate. Forward citations on included studies will be checked. Clinical Trials.gov and the Vista database will be searched for potentially eligible ongoing trials.

Data selection

The search results from each individual database will be saved in a master reference management library (EndnoteX7) and duplicates will be removed. Titles and abstracts of the citations retrieved by the literature search will be screened independently by two review authors (MOD, RG) for inclusion or exclusion using Rayyan QCRI. The full text of potentially relevant studies will be selected for further assessment and two independent authors will ascertain and agree on eligibility based on the full article (RG, MOD). Any disagreement regarding

inclusion will be resolved by discussion, or by referral to a third assessor (PB) if necessary.

Results of the screening process will be detailed in a PRISMA flow diagram.

Data extraction

Data will be extracted and entered into a standardised recording data extraction form. Data including author, study design, population characteristics (age, gender, type of stroke, severity of stroke), intervention characteristics (intervention type, intervention content, duration of intervention, method of delivery, setting of intervention, length of follow-up), control group (passive, active), primary and secondary outcomes at postinterventions and follow-up, when available, will be extracted.

Data including the severity of cognitive impairment, type of cognitive impairment (ie, domain(s) of cognition affected), neuropsychological underpinnings of cognitive impairment, means(assessment) of formal diagnosis of cognitive impairment, definition of cognition/cognitive impairment poststroke within each study, where available, will be extracted.

Both the stage poststroke (acute, subacute and chronic) and the severity of cognitive impairment (mild, moderate, severe) will be considered within the context of each individual study and reported descriptively. The theoretical basis of the intervention/mechanisms by which these interventions mediated cognitive improvement poststroke will also be documented. In consideration of the association between language impairments and performance on cognitive assessments, the language effects of primary outcome measures will be extracted.

Study authors will be contacted for missing data if necessary.

Risk of bias

The internal and external validity of studies will be assessed by two independent reviewers (MOD, SH) using the Cochrane Risk of Bias Tool in accordance with the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias and any other sources of bias.[23] Disagreements will be resolved by consensus among two other reviewers (RG, PB). Disagreements among the review authors on the methodological quality of the identified studies will be discussed and resolved by group consensus.

Strategy for data synthesis

We will perform separate analyses for trials comparing interventions to reduce cognitive impairment with 'treatment as usual', or with a 'placebo' control intervention, and trials comparing two active interventions. The Cochrane Review Manager software (RevMan) will be used to conduct statistical analyses to determine the treatment effect. For continuous data, we will calculate the treatment effect using mean differences (SMD) and 95% CI where different studies used different scales to assess the same outcome, and calculate SMD and 95% CI where studies have all used the same method of measuring outcome.

Due to the breadth of both interventions and cognitive outcome measures, it may be difficult to synthesise the data across studies. The impact of heterogeneity on results will be assessed using the I^2 statistic. When the I^2 is <30% there is little concern about statistical heterogeneity.[23] If there is statistical heterogeneity ≥50% we will use random-effects models to take account of the between-study variation in our findings.[23]

If meta-analysis is not possible as a result of substantial heterogeneity, a narrative synthesis of findings from the included studies will be provided.

Subgroup analysis

If a sufficient number of randomised controlled trials are identified, subgroup analyses will be conducted to establish the effect of the following subgroups on overall outcomes:

- Participant-related characteristics, for example, age of individuals with stroke (<65 vs >65); type and severity of stroke; time since stroke onset; severity of cognitive impairment; effect of depression and/ or fatigue on cognitive function; adherence to intervention.
- Intervention-related characteristics, for example, type of intervention: individual vs group training, self-efficacy training versus aerobic exercise training; impact of healthcare professionals on intervention outcomes; frequency, intensity, time and type of intervention.
- Outcome-related characteristics, for example, type of cognitive outcome assessed (including potential effects of language impairment on performance of the test), global cognitive outcome versus domain-specific outcome.

DISCUSSION

This systematic review and meta-analysis will use a rigorous methodology to provide up-to-date evidence regarding the effectiveness of all types of non-pharmacological rehabilitation interventions on cognitive function poststroke. Given the breadth of interventions shown to have an effect on poststroke cognitive impairment, there is a need to investigate all interventions, not solely cognitive rehabilitation interventions, which may mediate improvements in cognitive function poststroke. Previous research has taken a domain-specific approach to evaluating the effectiveness of cognitive rehabilitation interventions on cognitive deficits poststroke. Given the diffuse nature of poststroke cognitive impairment, the effectiveness of all types of non-pharmacological rehabilitation interventions across multiple domains of cognitive functioning poststroke needs to be investigated. A rigorous review of the effectiveness of all non-pharmacological rehabilitation interventions with regard to cognitive impairment poststroke is therefore needed.

The results of this review will inform the optimal type of intervention to rehabilitate cognitive impairment

poststroke including information on frequency, intensity, type and delivery of interventions. This information will inform the development of an optimal intervention to rehabilitate cognitive impairment poststroke. In addition, if data prove to be sufficiently homogenous to conduct a meta-analysis, information regarding the expected effect size associated with each intervention may be made available to healthcare professionals. This will be of use to clinicians and policy-makers in their design and evaluation of rehabilitation services aimed at improving cognitive impairment poststroke.

ETHICS AND DISSEMINATION

Findings will be disseminated through publication in peer-reviewed journals and through conferences. The rigorous scrutiny of primary studies will identify the strengths and limitations of current research and will provide recommendations for future research within this area.

Contributors MOD, PB and RG were major contributors in writing the manuscript. SH, PB and SC designed the overall study. MOD, PB and RG developed the search strategy. All authors critically appraised and edited the manuscript. SH is the guarantor of the review. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Findings will be disseminated through publication in peer-reviewed journals and through conferences. The rigorous scrutiny of primary studies will identify the strengths and limitations of current research and will provide recommendations for future research within this area.

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