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Efficacy and safety of hyperbaric oxygen therapy for Parkinson's disease with cognitive dysfunction: protocol for a systematic review and meta-analysis

Weiqiang Tan ,[1] Zhaoquan Pan,[1] Fengxi Xie[2]

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WT, ZP and FX are joint first authors.

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[1]Guangxi University of Chinese Medicine, Nanning, Guangxi, China
[2]Maoming Hospital of Guangzhou University of Chinese Medicine, Maoming, Guangdong, China

Correspondence to
Dr Weiqiang Tan;
791420012@qq.com

ABSTRACT

Introduction The presence of cognitive dysfunction notably affects the quality of life in individuals diagnosed with Parkinson's disease (PD) and is often recognised as a non-motor symptom. Comprehensive studies have shown the possible advantages of hyperbaric oxygen therapy (HBOT) in alleviating cognitive deficits in these individuals. This systematic review aims to investigate the practicality of incorporating HBOT within a more extensive therapeutic framework for PD, with a specific focus on cognitive symptoms.

Methods and analysis A comprehensive literature review will be conducted utilising various databases such as PubMed and Cochrane Library and so on. The duration of the search will encompass the entire timeline from the initiation of each database up to 1 April 2024. This investigation seeks to uncover randomised controlled trials that explore the efficacy and safety of HBOT in patients with PD who are facing cognitive impairments. The authors' autonomous screening and extraction of data will facilitate the attainment of impartial results. The assessment of possible biases will be conducted using the Cochrane risk-of-bias tool, while statistical analyses will be executed with RevMan V.5.3 and Stata V.15.0.

Ethics and dissemination As this review synthesises and evaluates previously conducted studies, the requirement for ethical approval is not applicable. The findings from this review will be shared via academic publications, comprehensive reports and presentations at pertinent conferences.

PROSPERO registration number CRD42024504763

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We plan to implement a thorough search strategy across eight databases.
⇒ This study provides a detailed evaluation of hyperbaric oxygen therapy's (HBOT) safety and efficacy in treating cognitive dysfunction in Parkinson's disease (PD), with the goal of aggregating and assessing current data to support evidence-driven conclusions.
⇒ Differences in session frequency, pressure intensity or treatment duration of HBOT may contribute to significant clinical heterogeneity across studies.
⇒ Limited existing research curtails a full understanding of HBOT's mechanisms of action in treating cognitive impairment associated with PD.

INTRODUCTION

Cognitive dysfunction serves as a significantly impairing non-motor aspect in Parkinson's disease (PD), encompassing mild cognitive impairment (PD-MCI) and PD dementia (PDD). Importantly, PD-MCI acts as an independent precursor to PDD.[1] Epidemiological findings reveal that up to 40% of individuals with PD display PD-MCI,[2] with a 30% incidence rate among newly diagnosed cases.[2] Furthermore, the occurrence of PDD stands at roughly 26.3%.[3] For those enduring PD for over a decade, the cumulative incidence of PDD escalates sharply to 75%,[4] and exceeds 20 years, it surges to 83%.[5] Cognitive impairment may emerge at any stage of PD[6 7] and exhibit substantial symptom variability.[8] Beyond cognitive challenges, individuals with PDD frequently suffer from diverse psychiatric and behavioural issues, including hallucinations, illusions, delusions, depression, emotional detachment and rapid eye movement sleep behaviour disorder, particularly prevalent are visual hallucinations and illusions.[9] The extensive prevalence and enduring nature of these symptoms drastically diminish the quality of life for those with PD, impose heavy burdens on families and caregivers and could potentially reduce life expectancy.[10 11]

At present, the mechanisms underlying PD and its association with cognitive dysfunction remain elusive, and there are no treatments available that alter the disease's trajectory.[12 13] Clinical trials primarily focused on PDD and PD-MCI have examined pharmacological agents originally developed for Alzheimer's disease (AD), including cholinesterase inhibitors and memantine, which acts as an antagonist of the N-methyl-D-aspartate receptor.[14] Unfortunately, the prolonged administration

Table 1 Search strategy for PubMed

Order	Terms
#1	"Hyperbaric Oxygenation"[MeSH Terms]
#2	"hyperbaric oxygenations"[Title/Abstract]OR "hyperbaric oxygen therapy"[Title/Abstract]OR "hyperbaric oxygen therapies"[Title/Abstract]OR "high pressure oxygen"[Title/Abstract]OR "oxygen therapy"[Title/Abstract]
#3	#1 OR #2
#4	"Parkinson Disease"[MeSH Terms]
#5	"Parkinson's Disease"[Title/Abstract]OR "Idiopathic Parkinson's Disease"[Title/Abstract]OR "Idiopathic Parkinson Disease"[Title/Abstract]OR "Lewy Body Parkinson's Disease"[Title/Abstract]OR "Lewy Body Parkinson Disease"[Title/Abstract]OR "Primary Parkinsonism"[Title/Abstract]OR "Paralysis Agitans"[Title/Abstract]
#6	#4 OR #5
#7	"Cognitive Dysfunction"[MeSH Terms]
#8	"Dementia"[MeSH Terms]
#9	"Cognitive Dysfunctions"[Title/Abstract]OR "Cognitive Impairments"[Title/Abstract]OR "Cognitive Impairment"[Title/Abstract]OR "Mild Cognitive Impairment"[Title/Abstract]OR "Mild Cognitive Impairments"[Title/Abstract]OR "Cognitive Disorder"[Title/Abstract]OR "Cognitive Disorders"[Title/Abstract]OR "Cognitive Decline"[Title/Abstract]OR "Cognitive Declines"[Title/Abstract]OR "Dementias"[Title/Abstract]OR "Amentia"[Title/Abstract]OR "Amentias"[Title/Abstract]
#10	#7 OR #8 OR #9
#11	"randomized controlled trial" [Publication Type]
#12	"controlled clinical trial" [Publication Type]
#13	"randomized"[Title/Abstract]OR "placebo"[Title/Abstract]OR "clinical trials as topic"[Title/Abstract]
#14	#11 OR #12 OR #13
#15	#3 AND #6 AND #10 AND #14

of these drugs frequently results in undesirable side effects, necessitating dosage adjustments or cessation.[15] Non-invasive brain stimulation techniques present a promising alternative for addressing cognitive dysfunction in PD[16 17]; yet their practical application is limited by technological complexities, concerns over effectiveness and substantial costs. Alternatively, kinesitherapy and cognitive rehabilitation are potential therapies that may ameliorate cognitive deficits in PD[18–24]; however, extensive research is still required to validate their efficacy, and logistical challenges may impede their broad implementation. Therefore, the urgent development of innovative, more effective and safer therapeutic approaches is paramount.

Hyperbaric oxygen therapy (HBOT) serves as a supplementary treatment, delivering 100% oxygen under conditions exceeding 1.4 atmospheres of pressure. Recent studies suggest that HBOT may alleviate symptoms of neurodegenerative disorders,[25 26] particularly cognitive decline.[27] Demonstrated to be effective in conditions such as MCI, AD and vascular dementia,[28–30] HBOT is gaining attention. In PD contexts, preclinical investigations have shown that HBOT might promote mitochondrial biogenesis via the SIRT-1/PGC-1α pathway.[31] From a clinical perspective, multiple studies have affirmed HBOT's efficacy in enhancing cognitive functions among PD patients, highlighting its potential as an adjunctive physical therapy. However, high-quality evidence supporting significant effects is still lacking. Therefore, this meta-analysis aims to comprehensively review previous clinical randomised controlled trials (RCTs) utilising HBOT for cognitive dysfunction among patients with PD to promote more reliable evidence-based clinical practice.

METHODS

Study registration

The protocol was developed following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols[32] and has been registered on PROSPERO (CRD42024504763).

Searching strategy

The eight databases that will be searched will be Embase, PubMed, Web of Science and Cochrane Library, which are all in English; China National Knowledge Infrastructure, China Science Periodical Database, Chinese Citation Database and China Biology Medicine disc, which are all in Chinese, will be searched in a thorough and exhaustive manner. All the way up to 1 April 2024, this search will cover every database from the start. In order to get all relevant studies, we will utilise these search terms: "hyperbaric oxygenation", "hyperbaric oxygen therapy", "high pressure oxygen", "oxygen therapy", "Parkinson Disease", "Idiopathic Parkinson's Disease", "Idiopathic Parkinson Disease", "Lewy Body Parkinson's Disease",

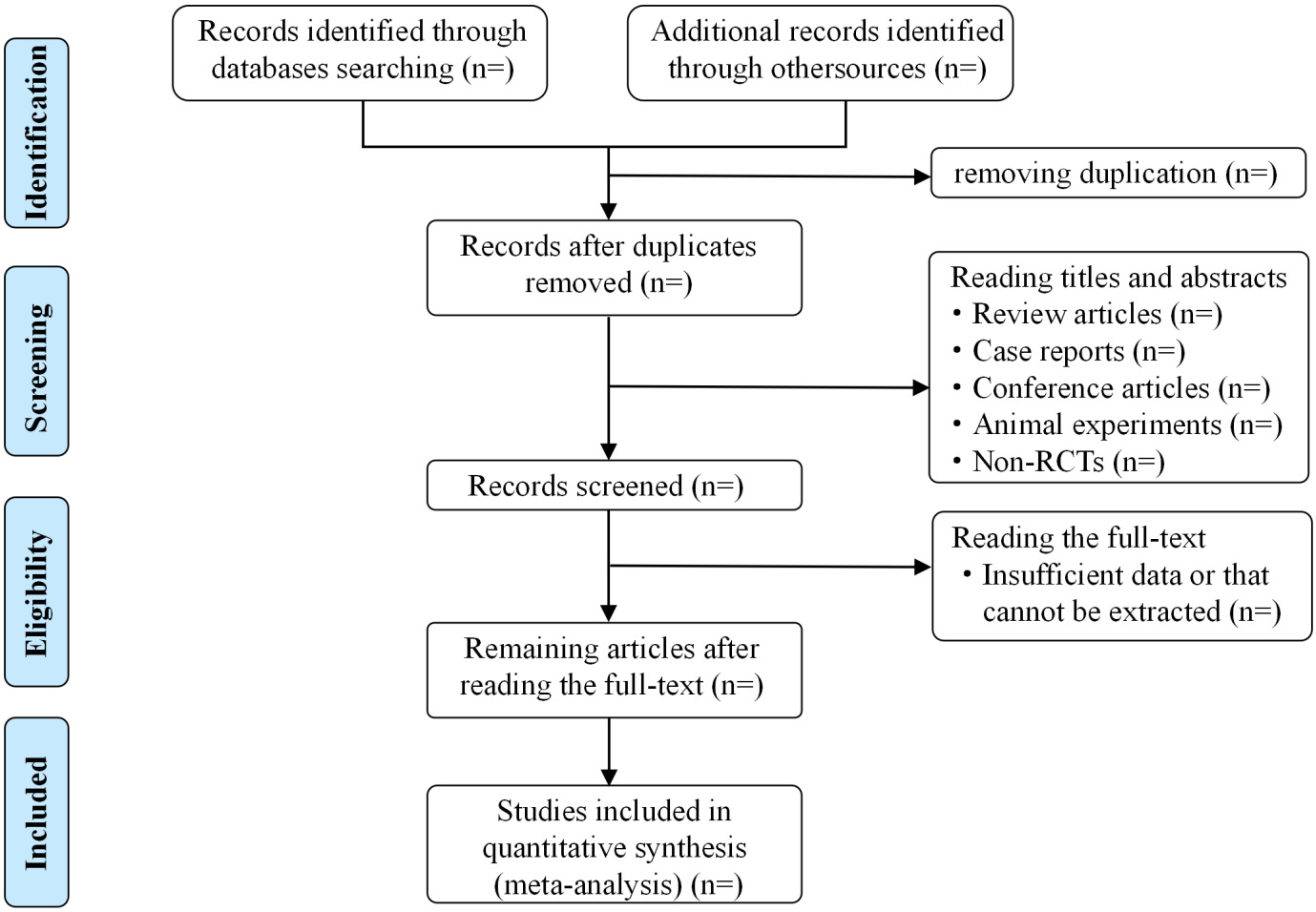

Figure 1 Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram of the study selection process. RCT, randomised controlled trial.

"Primary Parkinsonism", "Paralysis Agitans", "Cognitive Dysfunction", "Dementia", "Cognitive Impairment", "Cognitive Disorder", "Cognitive Decline", "Amentia", "Randomised controlled trial", "Controlled clinical trial", "Clinical trials as topic", '"Placebo". In order to facilitate searches in Chinese databases, these terms will be translated into Chinese. With the methods for other databases given in online supplemental eTables 1–7, table 1 presents the PubMed search technique. The study will start on 1 November and end on 31 December.

Eligibility criteria

Our evaluation will encompass study designs, participant demographics, intervention methodologies, comparative analyses, outcome measures, and the overall quality of the research. Each study will undergo rigorous screening to determine its eligibility for inclusion.

Types of study

RCTs reported in English or Chinese.

Types of participants

Inclusion criteria involve patients with PD-MCI or PDD according to any established diagnostic standards, including MDS clinical diagnostic criteria[33 34] and the China clinical diagnostic criteria.[9 35] Studies enrolling patients with PD who lack a definitive diagnosis of associated cognitive dysfunction, based on scales or assessment tools stipulated in the diagnostic standards, will be excluded. There will be no exclusion based on gender, age or disease duration.

Types of interventions

Patients in the study group received HBOT at their discretion, with no restrictions on the number of sessions, pressure levels or total treatment time.

Comparisons

1. Comparison of HBOT with placebo HBOT.
2. Comparison of HBOT with standard treatments as recommended by current guidelines, encompassing Western pharmaceuticals like antiparkinsonian and antipsychotic medications, surgical procedures such as deep brain stimulation and rehabilitative measures including cognitive training.
3. Assessment of HBOT combined with other treatments versus these treatments alone.
4. Evaluation of HBOT combined with other treatments versus placebo HBOT combined with these treatments.

Types of outcomes

Main results

The assessment tools employed encompass the PD Cognitive Rating Scale,[36] Montreal Cognitive Assessment,[37 38] Mattis Dementia Rating Scale-2,[39] Mini-Mental Parkinson,[40] Scales for Outcomes in PD-Cognition[40 41] and the Parkinson Neuropsychometric Dementia Assessment.[42]

Secondary results

1. The Movement Disorder Society-Unified PD Rating Scale assesses both motor and non-motor symptoms, along with daily living abilities in individuals with PD.
2. Tools utilised to assess quality of life encompass the WHO's Quality of Life Rating Scale and the Short-form 36.
3. Adverse events, such as ecchymoses, nausea or headaches, are systematically documented.

Data selection

The literature will be screened by two separate reviewers to reduce the possibility of subjective bias and to ensure that all relevant prospective RCTs are included. Using EndNote V.X9, we will first sort the literature from each database and remove any duplicates. The next step is to use predetermined criteria to screen the abstracts and titles. The remaining articles will be evaluated for eligibility after a thorough examination of their full texts. Both reviewers will share and cross-verify the chosen studies, resolving any differences either by reaching a mutual agreement or through the arbitration of a third reviewer. The process for selecting or excluding studies, including the reasoning and outcomes, will be methodically recorded and depicted in the PRISMA flowchart (figure 1).

Data extraction

Data will be rigorously extracted by two independent reviewers. This includes: fundamental study information (first author's name, date of publication, and duration); demographic and disease attributes of participants (sample size, age, gender, onset age of the disease, duration of PD, levodopa equivalent daily dosage[43] and level of cognitive impairment); intervention specifics (type, frequency, duration, dosage and hyperbaric oxygen pressure intensity); detailed records of adverse events and the outcome definitions employed in the study. Exclusions will be made for non-RCTs, review articles, animal research, case reports, conference papers and studies with inaccurate or incomplete data.

Risk of bias assessment

For the purpose of evaluating RCT quality, the Cochrane Risk of Bias 2.0 tool[44] will pay special attention to the following areas: overall bias, measurement of outcomes, reporting of results, missing outcome data, intervention adherence and random sequence generation. There will be three levels of risk: low, high and unclear. Research that is mainly considered to be 'low-risk' will be given priority. Quality and evidence assessments will be independently performed by two investigators, with resolutions made through discussion for any discrepancies.

Data synthesis and statistical analysis

Measures of treatment effect

Reviews will be conducted using the latest version of the Review Manager programme, which is 5.3. A 95% CI and pooled relative risk will be determined for binary outcomes by applying the Mantel–Haenszel technique. This study will use the inverse variance approach to assess continuous outcomes. For consistent measures, we will use the weighted mean difference and 95% CIs. For changing methods, we will use the standardised mean difference and 95% CIs. $P<0.05$ will be used to evaluate statistical significance.

Assessment of heterogeneity

To evaluate the variation or heterogeneity across studies, the I^2 statistic and p values will be employed. Heterogeneity will be considered acceptable when $I^2 \leq 50\%$ and $p \geq 0.1$, warranting the use of a fixed-effects model.[45–47] Conversely, significant heterogeneity is flagged by $I^2 > 50\%$ and $p < 0.1$, necessitating the adoption of a random-effects model.[45–47]

Assessment of reporting biases

Using Stata V.15.0 software, Egger's test will be applied to identify publication bias in analyses with more than 10 studies; a p value <0.05 will signify a significant bias. In order to assess the probable influence of the detected biases, the trim-and-fill technique will be used. In the article, any instances of publishing bias that are found will be thoroughly examined and explained.

Sensitivity analysis and subgroup analysis

On recognising significant variability within the analysis, we will explore possible sources through sensitivity and subgroup analyses. Sensitivity analyses will assess variables including sample size and risk of bias evaluations to gauge their influence on the aggregate outcomes. Furthermore, contingent on the availability of adequate data, subgroup analyses will be performed to determine if particular factors contribute to the variability in observed effects across studies. Participant-related variables to be scrutinised encompass ethnic background, PDD severity, disease duration and various treatment parameters. Interventions will be analysed based on type, frequency, duration, dosage and the intensity of hyperbaric oxygen pressure.

Confidence in cumulative evidence

Two writers used the GRADE framework in conjunction with the GRADEPro software[48] to autonomously assess the evidence's certainty. Factors including publication bias, precision, honesty, heterogeneity and risk of bias were taken into account in this evaluation. Each level of evidentiary certainty—high, medium, low, and extremely low—reflects the strength of the evidence. When discrepancies

arose between reviewers, a third evaluator was engaged to mediate and resolve these differences.

Patient and public involvement

None.

Ethics and dissemination

Ethical approval was not required. The results of the review will be disseminated through publications, reports and conference presentations.

Contributors WT and ZP originated the research and devised its methodologies. ZP and FX formulated the search approach. WT drafted the initial manuscript. WT supervised the implementation of the entire project. WT is the guarantor. No, I have not used AI.

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ORCID iD

Weiqiang Tan http://orcid.org/0000-0003-3009-0214

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