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Hyperbaric Oxygen Therapy Improves Motor Symptoms, Sleep, and Cognitive Dysfunctions in Parkinson's Disease

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Keywords
Hyperbaric oxygen · Parkinson's disease · Sleep disorder · Cognitive dysfunction · Meta-analysis

Abstract
Introduction: The aim of the study was to systematically analyze the therapeutic effectiveness of hyperbaric oxygen therapy compared with conventional drug therapy in patients with Parkinson's disease. ***Methods:*** PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Database searched to the end of March 2023. Two authors independently screened and abstracted data from each trial. The primary outcome measures included the efficacy rate and the Unified Parkinson's Disease Rating Scale III (UPDRS III). Secondary outcome measures included the Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Hamilton Depression Scale (HAMD), Minimum Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Hoehn-Yahr staging. ***Results:*** Thirteen studies with a total of 958 participants were included in the meta-analysis. After intervention, the experimental group exhibited a higher treatment efficacy rate compared to the control group (odds ratio = 3.18, 95% confidence interval [95% CI; 1.60, 6.33], $p < 0.01$), a lower UPDRS III score (mean difference [MD] = −2.96, 95% CI [−4.31, −1.61], $p < 0.01$), and lower Hoehn-Yahr staging (MD = −0.14, 95% CI [−0.26, −0.02], $p < 0.01$). The experimental group also outperformed the control group in non-motor symptoms, with higher scores in MoCA, PSQI, and ESS (standardized MD = 0.65, 95% CI [0.45, 0.85], $p < 0.01$), (MD = −2.52, 95% CI [−2.85, −2.18], $p < 0.01$), and (MD = −3.30, 95% CI [−3.77, −2.83], $p < 0.01$), respectively. ***Conclusion:*** Hyperbaric oxygen therapy improves motor function, relieves the severity of the disease, ameliorates cognitive function, and improves sleep quality while alleviating excessive daytime sleepiness in patients with Parkinson's disease. The therapeutic mechanism of hyperbaric oxygen therapy may be related to increased cerebral tissue oxygen content, which contributes to anti-hypoxic, anti-inflammatory, anti-apoptotic, and antioxidant stress.

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Introduction

Parkinson's disease (PD) is a rapidly progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra of the midbrain [1]. The prevalence increases sharply with age, and the incidence was 1.7% in people above 65 years of age in China [2]. Clinical symptoms of PD primarily display bradykinesia, resting tremors, muscle rigidity, balance and gait abnormalities, along with non-motor symptoms such as depression, anxiety, cognitive impairment, sleep disturbances,

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and autonomic dysfunction [3]. In the advanced stages, most patients may become bedridden or disabled, imposing a heavy burden on families and society. Currently, both levodopa medication and deep brain stimulation surgery can alleviate motor symptoms to some extent. However, they fail to slow or halt disease progression [4]. In recent years, hyperbaric oxygenation (HBO) therapy has been employed to treat over 100 diseases, including stroke, traumatic brain injury, and carbon monoxide poisoning [5]. Although HBO may exert therapeutic effects on PD by increasing cerebral tissue oxygen content, ameliorating hypoxia, and consequently inhibiting the loss of dopaminergic neurons in the substantia nigra, promoting functional recovery [6, 7], its clinical efficacy and specific mechanisms remain unclear. For instance, in the case of a PD patient with severe depression and anxiety who refused treatment with dopamine agonists or selective serotonin reuptake inhibitors (SSRIs), a 30-day course of HBO therapy showed improvement in scores for depression and anxiety, including the Unified Parkinson's Disease Rating Scale I (UPDRS I), UPDRS II, the Hamilton Depression Rating Scale, and the Hamilton Anxiety Rating Scale. These findings suggest that HBO may be a potential therapeutic method for PD patients suffering from depression and anxiety. This study aimed to perform a meta-analysis to assess the published clinical research data on HBO therapy for PD and ascertain its therapeutic efficacy, laying the foundation for its potential application in treating neurodegenerative diseases such as PD.

Methods

Search Strategy and Selection Criteria

The search time was from the establishment of the database to March 2023, and the search language was English and Chinese: Medical Subject Heading terms for Parkinson disease, Idiopathic Parkinson's Disease, Lewy Body Parkinson's Disease, Parkinson's Disease (Idiopathic), Parkinson's Disease (Lewy Body), Parkinson Disease (Idiopathic), Parkinson's Disease, Idiopathic Parkinson Disease, Lewy Body Parkinson Disease, Primary Parkinsonism, Parkinsonism (Primary), Paralysis Agitans; and Hyperbaric Oxygenation, Hyperbaric Oxygenations, Oxygenations (Hyperbaric), Hyperbaric Oxygen Therapy, Hyperbaric Oxygen Therapies, Oxygen Therapies (Hyperbaric), Oxygen Therapy (Hyperbaric), (Therapies) Hyperbaric Oxygen, (Therapy) Hyperbaric Oxygen, Oxygenation (Hyperbaric); we identified relevant trails by electronic searches of general biomedical and science electronic databases (PubMed, Web of science, Cochrane); Chinese databases (China National Knowledge Infrastructure [CNKI] and Wanfang database) were searched with [(帕金森病 translate as "Parkinson's disease" or 老年病 translate as "geriatric" or 遗传型帕金森病 translate as"Hereditary Parkinson's disease") and (高压氧 translate as "Hyperbaric Oxygen Therapy" or 高压混合氧 translate as "High pressure mixed oxygen" or 医用高压氧 translate as "Medical Hyperbaric oxygen")]). The data that support the findings of this study are openly available in Chinese journal databases CNKI and Wanfang database at https://www.cnki.net/; https://www.wanfangdata.com.cn/, reference number [8–20].

Inclusion criteria included the following: (1) study type: randomized controlled trials (RCTs) of HBO therapy for PD published in China and abroad; (2) participants: patients clinically diagnosed with PD [21]; (3) interventions: the experimental group received HBO in addition to standard drug therapy; (4) comparison: the control group received standard drug therapy alone; (5) outcome indicators: primary outcome indicators were as follows – ① efficacy of HBO therapy for PD, assessed using the Webster Scoring Scale (a reduction of 11% or more in the total score after treatment compared to before treatment was considered "effective," while the rest were considered "ineffective") [8], ② motor function, assessed using Part III of the Unified Parkinson's Disease Rating Scale (UPDRS), ③ Disease severity grading, assessed using Hoehn-Yahr staging; secondary outcome indicators include the following: ① non-motor symptoms, evaluated using the Non-Motor Symptom Questionnaire for Parkinson's Disease (NMSQ), ② sleep-related assessments, measured using the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS), ③ mental state, assessed using the Hamilton Depression Scale (HAMD), ④ cognitive function, evaluated using the Minimum Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA).

Exclusion criteria included the following: (1) duplicate publications (selecting the earliest publication); (2) review articles or meta-analyses; (3) case reports; (4) animal studies or experiments; (5) conference literature; (6) not relevant studies; (7) non-randomized controlled trials (RCTs); (8) inaccessible full-text articles; (9) studies that involve other interventions during the trial, such as deep brain stimulation therapy; (10) primary outcomes that are not relevant.

Literature Screening and Quality Assessment

Two researchers independently screened the literature search results based on the inclusion and exclusion criteria, which included evaluating the titles and abstracts of the retrieved articles. Subsequently, full-text reading was

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conducted to identify high-quality RCT studies and primary outcome measures. In case of disagreements, a third researcher was consulted to reach a consensus, and ultimately, the eligible articles were determined. A predesigned data extraction form was used by one researcher to extract relevant data, and a second researcher verified the information extracted. The methodological quality and risk of bias in the included RCT studies were assessed using the modified Jadad scoring scale and Cochrane risk of bias assessment tool. The Jadad scoring scale ranges from 0 to 5 points, with studies scoring ≤2 points considered low-quality clinical research and those scoring >2 points considered high-quality clinical research. Specific evaluation items included (1) generation of random sequence, (2) blinding method, and (3) withdrawals and dropouts. The Cochrane risk of bias assessment covered the following aspects: (1) sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) completeness of outcome data; (6) selective reporting of outcomes; (7) other sources of bias.

Data Synthesis

Meta-analyses were performed using RevMan 5.4 software. For dichotomous outcome measures, the effect size was expressed as odds ratios. For continuous outcome measures with different scales, the effect size was standardized mean difference (MD), and if the scales were the same, MD was used for analysis. Additionally, 95% confidence interval (95% CI) were calculated for the effect sizes. When outcome measures were comparable or similar between the experimental and control groups, a meta-analysis was conducted. If the heterogeneity among the effects was small ($I^2 \leq 50\%$), a fixed-effect model was employed for meta-analysis; however, if significant heterogeneity was observed ($I^2 > 50\%$, $p \leq 0.10$), a random-effect model was used for pooled analysis [22]. Descriptive analysis was utilized when meta-analysis was not feasible with the included data. A significance level of $p < 0.05$ was considered statistically significant. This study primarily analyzed the comparison between interventions with HBO (experimental group) and standard drug therapy (control group) by comparing the data from baseline to 1–3 months after treatment.

Results

Search Results

Of 262 potentially relevant studies identified, 71 duplicates were excluded by Endnote software, and 156 publications that clearly did not meet the inclusion criteria were excluded after reading the titles and abstracts. Following a full-text review, 22 articles were excluded, resulting in a final inclusion of 13 articles, including 1 conference article [13] and 12 journal articles, after excluding those whose study design did not meet the inclusion criteria (4), those with missing study data (1), those whose control group did not meet the inclusion criteria (14), and those with different main outcome indicators (3) by reviewing the full text and quality evaluation. The literature screening process and results are shown in Figure 1.

Basic Information of the Literature

This study included a total of 13 articles published between 1995 and 2022, all of which were conducted in China. The combined sample size was 958 participants, with 496 in the experimental group and 462 in the control group. Among the 13 studies, 11 clearly specified the inclusion and exclusion criteria for the participants. The experimental group received intervention with HBO, and details regarding the baseline characteristics and application protocols of the experimental group's HBO intervention can be found in Table 1, alongside key factors such as pressure levels, oxygen concentrations, and treatment duration in Table 2. The control group received conventional drug therapy, primarily including levodopa compound (madopar) and dopamine receptor agonists (pramipexole). In one trial [8], neurotrophic drugs were added to madopar, while in two other trials [9, 10], piracetam to improve brain metabolism, nimodipine to enhance cerebral blood flow, and vinpocetine as a vasodilator was administered in addition to madopar and anti-thrombotic drug, verapamil. Regarding the diagnostic criteria for PD, one study [8] did not specify the diagnostic basis of the included participants, while the remaining 12 experiments utilized the diagnostic criteria formulated in China [21]. The basic characteristics of the included literature are presented in Table 3.

Quality Evaluation and Risk Assessment

All included articles mentioned the use of random allocation, with six articles [11, 16–20] employing random number table allocation and 7 articles not specifically describing the method of random sequence generation. Each article reported consistent similarity among groups at baseline. One study [8] details the number and reasons for participant withdrawals. Due to the inherent challenges of implementing double-blinding in HBO interventions, the overall quality of the literature, as assessed by the Jadad score, was relatively low (see Fig. 2). Considering the unique nature of the experimental interventions, despite the lower Jadad scores in the included literature, it met the research requirements.

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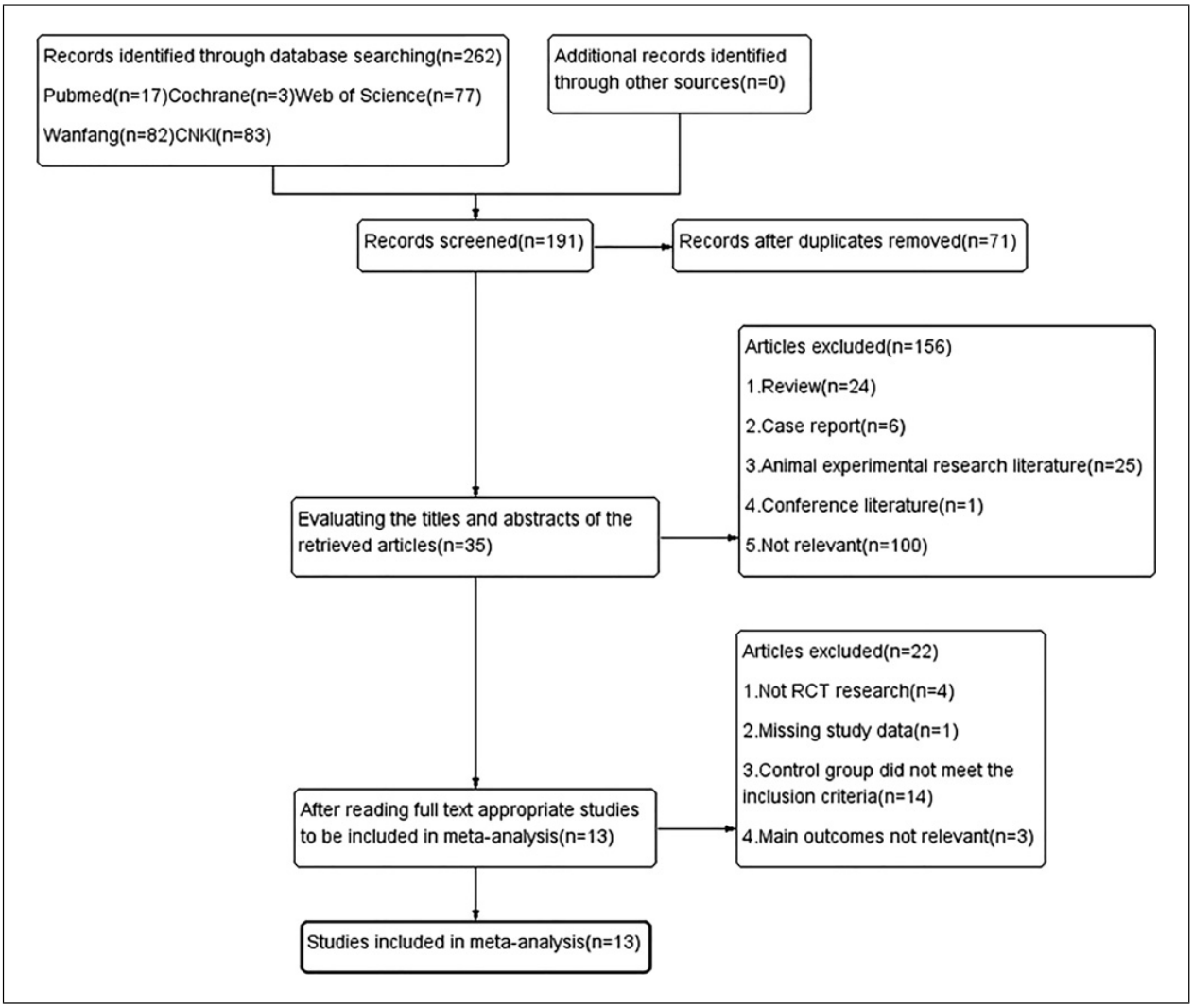

Fig. 1. Flow chart of literature screening.

Meta-Analysis Results

The Efficient Rate of HBO for PD

Four articles used the Webster Scoring method for pre- and post-treatment efficacy assessment, and there was no significant statistical heterogeneity among the included studies ($p = 0.78$, $I^2 = 0\%$, Fig. 3). Therefore, a fixed-effect model was employed for the meta-analysis. The results revealed a significant improvement in the efficacy rate in the experimental group (90.91%) compared to the control group (76.19%), with a statistically significant difference (odds ratio = 3.18, $p < 0.01$, Table 4).

Motor Function and Disease severity (H-Y)

Nine articles evaluated the effects of HBO therapy on motor function in patients with PD, and five articles used the Hoehn-Yahr classification to evaluate the severity of PD.

1. Motor function: nine articles used Part III of the UPDRS questionnaire to assess the motor function of the participants, and there was significant statistical heterogeneity among the studies ($p < 0.01$, $I^2 = 77\%$, Fig. 4). Therefore, a random-effect model was employed for the meta-analysis. The results showed that the experimental group had an average reduction of

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Table 1. HBO application population baseline and application scheme

First author	Mean age, years	Gender (male), %	Mean duration of PD, years	Duration of trial period
Chen et al. [8] (2024)	68.4	79	5.5	1–7 weeks
Zhang et al. [9] (2024)	61.4	66	5.2	8 weeks
Liu [10] (2011)	61.6	60	–	8 weeks
Liu [11] (2016)	61.4	52	3.8	8 weeks
Pan et al. [12] (2017)	60.3	50	3.2	8 weeks
Qi and Gu [13] (2017)	65.5	60	1.1	3 weeks
Wang [14] (2017)	62.8	60	3.3	8 weeks
Liu et al. [15] (2018)	65.2	53	3.5	8 weeks
Cheng [16] (2024)	68.1	60	–	8 weeks
Chen et al. [17] (2024)	68.9	53	–	4 weeks
Peng et al. [18] (2020)	68.2	59	3.6	7 weeks
Wang and Feng [19] (2021)	67.7	60	5.8	3 months
Zheng et al. [20] (2022)	59	50	3.8	8 weeks

2.96 points in UPDRS-III scores compared to the control group, indicating improved limb motor function in the participants, with a statistically significant difference ($p < 0.01$, Table 4).

2. Disease severity grading: five articles utilized Hoehn-Yahr (H-Y) grading to assess patients' progression of PD. As there was no statistical heterogeneity observed among the included studies ($p = 1.00$, $I^2 = 0\%$, Fig. 5), a meta-analysis was conducted using a fixed-effects model. The results revealed that the experimental group showed an average reduction of 0.14 points in the Hoehn-Yahr staging compared to the control group, and this difference was statistically significant ($p < 0.01$, Table 4).

Non-Motor Symptoms

Ten articles evaluated the effects of HBO on non-motor symptoms (sleep, depression, cognitive level) in patients using different scales.

1. Non-motor symptom questionnaire: two articles [17, 19] utilized the NMSQ questionnaire to measure patients' non-motor symptoms. The results indicated that the NMSQ scores were significantly lower in the experimental group when compared to the control group. These findings suggest that HBO therapy demonstrates effectiveness in ameliorating the non-motor symptoms of individuals afflicted with PD.
2. Sleep quality: five articles utilized the PSQI scale to measure the sleep quality of the participants, and there was no significant statistical heterogeneity among the included studies ($p < 0.01$, $I^2 = 87\%$, Fig. 6). Thus, a fixed-effect model was applied to the meta-analysis. The results showed that the experimental group had an average reduction of 2.52 points in the PSQI scale score compared to the control group, indicating an improvement in sleep quality, and this difference was statistically significant ($p < 0.01$, Table 4). Similarly, five articles used the ESS scale to assess the participants' excessive daytime sleepiness, and there was no significant statistical heterogeneity among the studies ($p = 1.00$, $I^2 = 0\%$, Fig. 7). A fixed-effect model was used for the meta-analysis. The results demonstrated that the experimental group had an average reduction of 3.30 points in the ESS score compared to the control group, suggesting a decrease in excessive daytime sleepiness in the participants, and this difference was statistically significant ($p < 0.01$, Table 4).
3. Depression: one article [19] used the HAMD to measure the participants' level of depression. The results indicated that the HAMD scores in the experimental group significantly decreased compared to the control group, suggesting that HBO therapy may be effective in improving depression in patients with PD. However, due to the limited number of studies available, statistical analysis could not be conducted.
4. Cognitive level: among the three articles, one utilized the MoCA score. At the same time, the other two employed the MMSE questionnaire and MoCA score to measure the participants' cognitive level. There was no

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Table 2. HBO application parameters and outcomes

First author	Type of HBO	Oxygen concentration, %	Pressure, ATA	Outcome
Chen et al. [8] (2024)	Classical HBO	–	2.3	①
Zhang et al. [9] (2024)	Classical HBO	–	2.0	②
Liu [10] (2011)	Classical HBO	100	2.5	①
Liu [11] (2016)	Classical HBO	100	2.0	②③
Pan et al. [12] (2017)	Classical HBO	100	2.0	②③
Qi and Gu [13] (2017)	Classical HBO	100	2.5	①
Wang [14] (2017)	Classical HBO	100	/	②③
Liu et al. [15] (2018)	Classical HBO	100	2.0	②③
Cheng [16] (2024)	Classical HBO	100	2.5	①②③
Chen et al. [17] (2024)	Classical HBO	–	2.5	②③
Peng et al. [18] (2020)	–	–	–	③
Wang and Feng [19] (2021)	Classical HBO	100	2.0	②③
Zheng et al. [20] (2022)	Classical HBO	100	2.0	②③

HBO, hyperbaric oxygen therapy. Outcome indicators: ① is the efficiency rate, ② is motor function, ③ is non-motor symptoms.

significant statistical heterogeneity among the included studies ($p = 0.72$, $I^2 = 0\%$, Fig. 8), so a fixed-effect model was used for the meta-analysis, and the standardized MD method was used to combine the effect sizes due to the use of different scales. The results showed that the experimental group had an average increase of 2.52 points in MoCA scores and MMSE questionnaire scores compared to the control group, indicating that HBO therapy is effective in improving cognitive function in patients with PD, and this difference was statistically significant ($p < 0.01$, Table 4).

HBO Side Effects

Three articles [14, 15, 18] have reported adverse reactions following HBO intervention. Out of these, two articles [14, 18] provided detailed descriptions of the adverse reactions and conducted statistical analysis to compare the incidence of adverse reactions between the test and control groups. However, the results did not show any statistically significant differences.

Discussion

HBO therapy, as a physical treatment method, has demonstrated significant efficacy in treating neurological disorders such as stroke, traumatic brain injury, carbon monoxide poisoning, and spinal cord injuries. In recent years, it has been increasingly studied as an adjuvant treatment for neurodegenerative diseases like Alzheimer's disease [23] and PD [24]. To further clarify its efficacy in PD treatment, this study employed a meta-analysis for the first time to rigorously combine and systematically evaluate relevant randomized controlled trials (RCTs). The results indicate that the combination of conventional drug therapy and HBO not only alleviates the motor symptoms of PD patients but also significantly improves non-motor symptoms, including sleep disturbance, excessive daytime sleepiness, and cognitive dysfunction. Considering previous literature, we speculate that HBO may exert its effects in PD by inhibiting abnormal aggregation of alpha-synuclein, oxidative stress, mitochondrial dysfunction, apoptosis, inflammation, and other related mechanisms to protect or repair damage to dopaminergic neurons in the substantia nigra.

Although the specific pathological mechanisms and etiology of PD are not yet fully understood, genetic, environmental factors, age, and brain injuries have been identified as risk factors for PD. Interestingly, these risk factors can all impair oxygen intake and utilization [25]. For instance, genetic factors can cause mitochondrial dysfunction, leading to impaired oxygen utilization. Aging is associated with a decrease in systemic oxygen utilization across multiple organs, putting PD patients in

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Table 3. Basic characteristics of the included studies

First author	Published year	Sample size (cases)		Intervention methods		Outcome
		EG	CG	EG	CG	
Chen et al. [8] (2024)	1995	53	57	HBO + basic therapy	Basic therapy	①
Zhang et al. [9] (2024)	2009	38	30	HBO + basic therapy	Basic therapy	②
Liu [10] (2011)	2011	30	30	HBO + basic therapy	Basic therapy	①
Liu [11] (2016)	2016	30	30	HBO + basic therapy	Basic therapy	②③
Pan et al. [12] (2017)	2016	20	20	HBO + basic therapy	Basic therapy	②③
Qi and Gu [13] (2017)	2017	10	10	HBO + basic therapy	Basic therapy	①
Wang [14] (2017)	2017	30	25	HBO + basic therapy	Basic therapy	②③
Liu et al. [15] (2018)	2018	45	45	HBO + basic therapy	Basic therapy	②③
Cheng [16] (2024)	2019	50	50	HBO + basic therapy	Basic therapy	①②③
Chen et al. [17] (2024)	2020	60	60	HBO + basic therapy	Basic therapy	②③
Peng et al. [18] (2020)	2020	34	34	HBO + basic therapy	Basic therapy	③
Wang and Feng [19] (2021)	2021	40	40	HBO + basic therapy	Basic therapy	②③
Zheng et al. [20] (2022)	2022	31	31	HBO + basic therapy	Basic therapy	②③

HBO, hyperbaric oxygen therapy; EG, experimental group; CG, control group. Outcome indicators: ① is the efficiency rate, ② is motor function, ③ is non-motor symptoms.

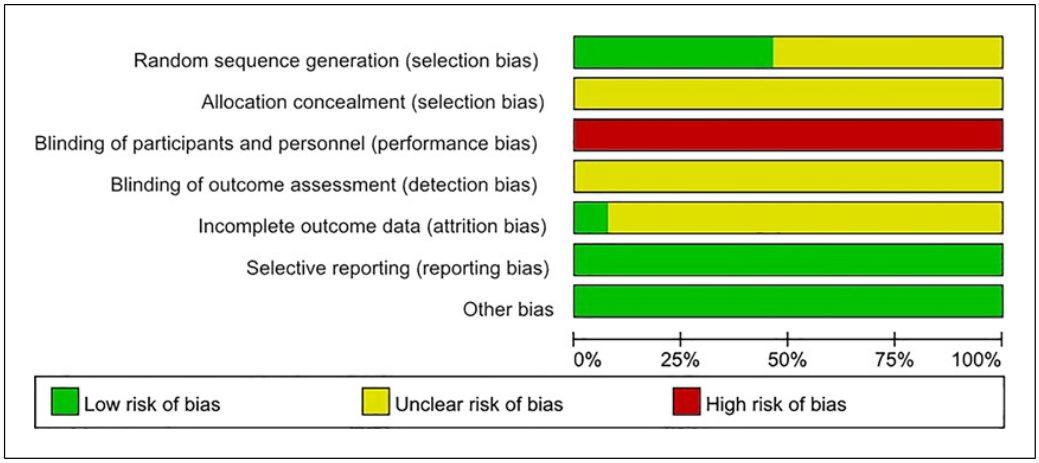

Fig. 2. Risk of bias for included studies.

a state of hypoxia. Therefore, hypoxia is considered to be closely related to the pathological development of PD. Studies have indicated that hypoxia can increase abnormal aggregation of alpha-synuclein (α-syn), inducing its neurotoxicity and accelerating the death of dopaminergic neurons [26]. Reduced regional cerebral blood flow caused by hypoxia can also result in impaired cognitive function. An increasing number of clinical studies have confirmed that daily HBO therapy has neurotherapeutic effects. It not only improves cognitive function in patients with cognitive impairments after stroke, traumatic brain injury, and hypoxia-induced brain injury but also

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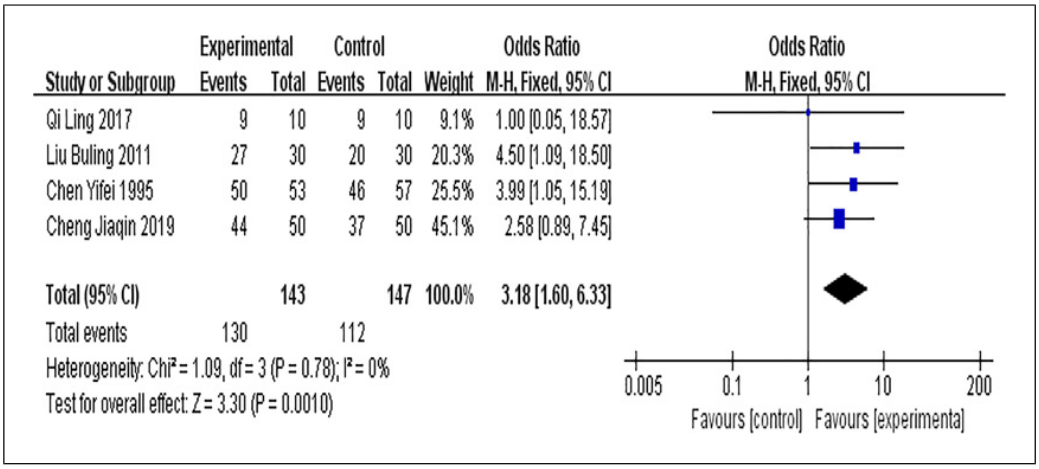

Fig. 3. Comparison of HBO interventions with control in relation to the efficient rate for PD.

Table 4. HBO application parameters and outcomes

First author	Type of HBO	Oxygen concentration, %	Pressure, ATA	Outcome
Chen et al. [8] (2024)	Classical HBO	–	2.3	①
Zhang et al. [9] (2024)	Classical HBO	–	2.0	②
Liu [10] (2011)	Classical HBO	100	2.5	①
Liu [11] (2016)	Classical HBO	100	2.0	②③
Pan et al. [12] (2017)	Classical HBO	100	2.0	②③
Qi and Gu [13] (2017)	Classical HBO	100	2.5	①
Wang [14] (2017)	Classical HBO	100	/	②③
Liu et al. [15] (2018)	Classical HBO	100	2.0	②③
Cheng [16] (2024)	Classical HBO	100	2.5	①②③
Chen et al. [17] (2024)	Classical HBO	–	2.5	②③
Peng et al. [18] (2020)	–	–	–	③
Wang and Feng [19] (2021)	Classical HBO	100	2.0	②③
Zheng et al. [20] (2022)	Classical HBO	100	2.0	②③

HBO, hyperbaric oxygen therapy. Outcome indicators: ① is the efficiency rate, ② is motor function, ③ is non-motor symptoms.

significantly improves attention, information processing speed, and executive function in healthy elderly individuals [27, 28]. There are two possible mechanisms for this effect. First, HBO therapy can increase the oxygen content in blood, elevate blood oxygen tension, and accelerate cerebral blood flow, compensating for the lack of oxygen in the brain. This helps the ischemic brain region receive more blood and oxygen supply, improving cognitive function and promoting the recovery of dopamine neurons affected by hypoxia. Additionally, increased cerebral blood flow can enhance drug absorption and improve the therapeutic effect on motor symptoms such as tremors, bradykinesia, and muscle rigidity [29]. Second, intermittent exposure to high levels of oxygen induced by HBO therapy leads to the release of hypoxia-inducible factor (HIF) and increases its stability and

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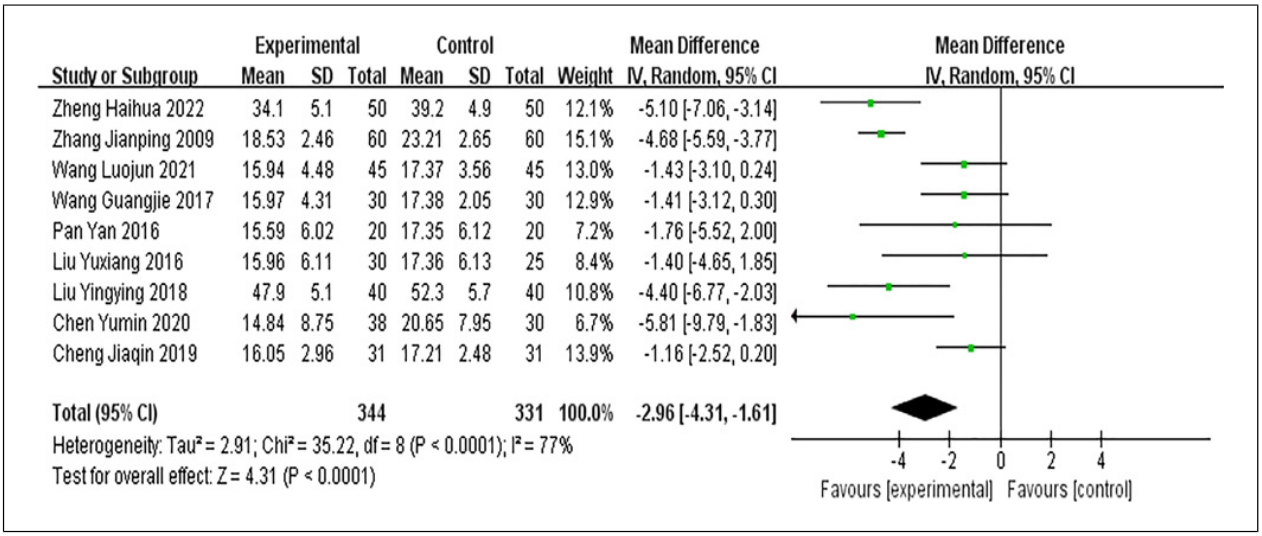

Fig. 4. Comparison of HBO interventions with control in relation to UPDRS questionnaire scores.

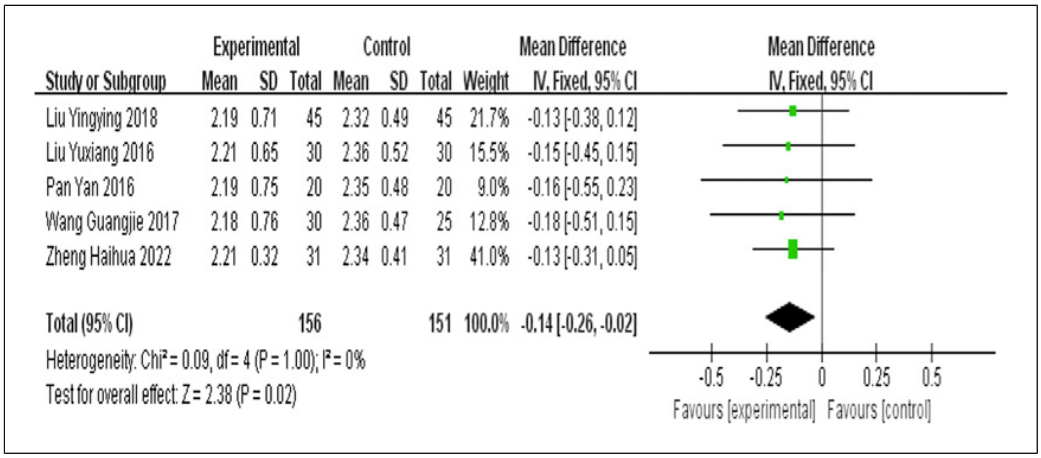

Fig. 5. Comparison of HBO interventions with control in relation to H-Y classification.

activity [30]. HIF-1α and HIF-2α can also regulate the release of vascular endothelial growth factor [31, 32], which can induce endothelial cells to recruit and differentiate into new blood vessels from existing ones [33]. This process increases local cerebral blood flow, thereby improving cognitive function in patients. It is worth noting that downstream target genes of one subunit of HIF-1α (EPO, vascular endothelial growth factor) have been shown to protect neurons in PD patients from damage [34] and are considered potential targets for PD drug therapy. Some studies have suggested that HBO may increase the secretion of peripheral adrenal-dopamine by stimulating the sympathetic-adrenal medullary system, thereby regulating the function of the sympathetic nervous system and improving autonomic nervous disorders such as orthostatic hypotension in PD patients [19].

On the other hand, oxidative stress mediated by reactive oxygen species plays a crucial role in dopaminergic neuron injury [35]. Malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GSH-Px) are commonly used indicators to evaluate oxidative stress response in the body. MDA levels are associated with

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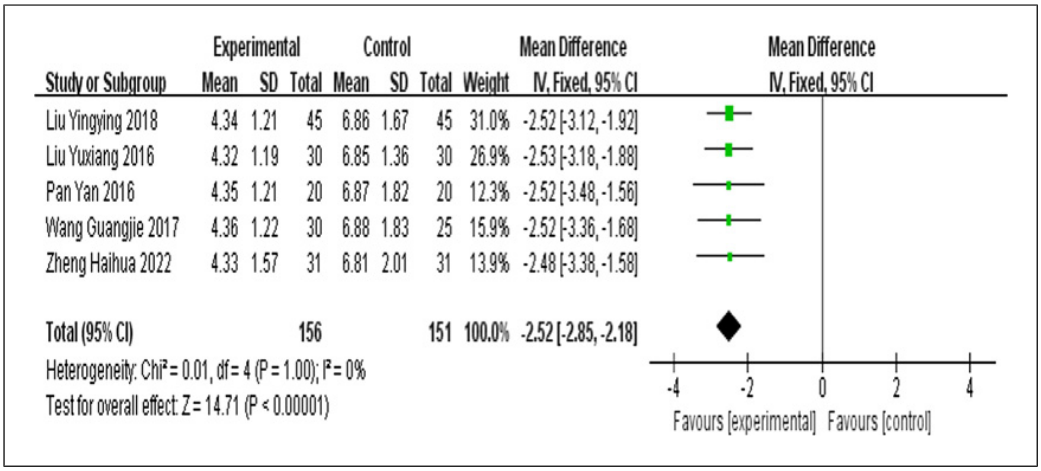

Fig. 6. Comparison of HBO interventions with control in relation to PSQI.

increased release of reactive oxygen species, which can impact blood vessels and cellular functions. Therefore, higher MDA levels indicate more severe oxidative stress. SOD and GSH-Px are key enzymes involved in combating oxidative stress and reducing cell membrane damage. Studies have shown that markers of oxidative damage, such as 4-hydroxynonenal (4-HNE), are elevated in the brains of PD patients, with decreased GSH-Px levels, leading to impaired dopamine secretion and neuronal damage [35]. However, continuous HBO therapy (once a day, 10 sessions as one course) can activate SOD, GSH-Px, and catalase activities, as well as activate important transcription factors involved in regulating cellular oxidative stress response, such as Nuclear factor erythroid 2-related factor 2 (Nrf2) and hypoxia-inducible factor-1α (HIF-1α), along with its target protein HO-1, which can reduce cytochrome c release and alleviate oxidative stress damage [36, 37]. Moreover, mitochondrial complex I activity has been reported to be reduced in the substantia nigra cells of PD patients [38], leading to energy metabolism disorders and increased production of superoxide anions, resulting in neuronal degeneration and death. HBO therapy can enhance mitochondrial ATPase activity, accelerate the electron transfer process, and restore energy supply in brain neurons.

Apoptosis is excessively activated during PD progression [39, 40]. Post-mortem studies of PD patients' brains have detected morphological features of apoptosis, such as cell shrinkage, chromatin condensation, and DNA fragmentation [39]. As previously mentioned, increased HNE levels in the brains of PD patients can activate key substances involved in apoptosis, such as caspase family proteases, leading to aggravated apoptosis. HBO therapy also plays a crucial role in regulating apoptosis, and the main mechanism is the hypothesis that HBO induces mitochondrial function. The ratio of pro-apoptotic Bax to anti-apoptotic Bcl-2/Bcl-xl can serve as the threshold for apoptosis susceptibility [41], which competitively regulates mitochondrial membrane permeability. Animal experiments have observed that HBO significantly increases Bcl-2 levels without affecting Bax, thereby reducing the Bax/Bcl-2 ratio and exhibiting anti-apoptotic effects [42]. In the intrinsic pathway of apoptosis, mitochondria release apoptotic factors such as cytochrome c into the cytoplasm. HBO can reduce cytochrome c expression and, therefore, decrease apoptosis.

In addition, inflammation has been linked to various neurodegenerative diseases, including PD [43]. It has been shown that PD patients have elevated levels of pro-inflammatory cytokines (IL-1β, IL-12, IL-6, TNFα, IFNγ) in their serum and cerebrospinal fluid, while anti-inflammatory cytokine (IL-10) levels are decreased [44, 45]. Regarding motor symptoms, studies have indicated that IL-6 levels are significantly higher in PD patients compared to healthy elderly individuals, and these elevated levels of IL-6 may accelerate muscle catabolism, leading to muscle reduction and causing patients to feel weak and fatigued; Scalzo et al. [46] found that PD patients with higher serum IL-6 levels performed worse in the Timed Up and Go Test (TUG). Moreover, higher levels of IL-4 and lower levels of IFNγ have been shown to significantly predict more severe tremors in PD patients [47], suggesting a potential correlation between PD motor

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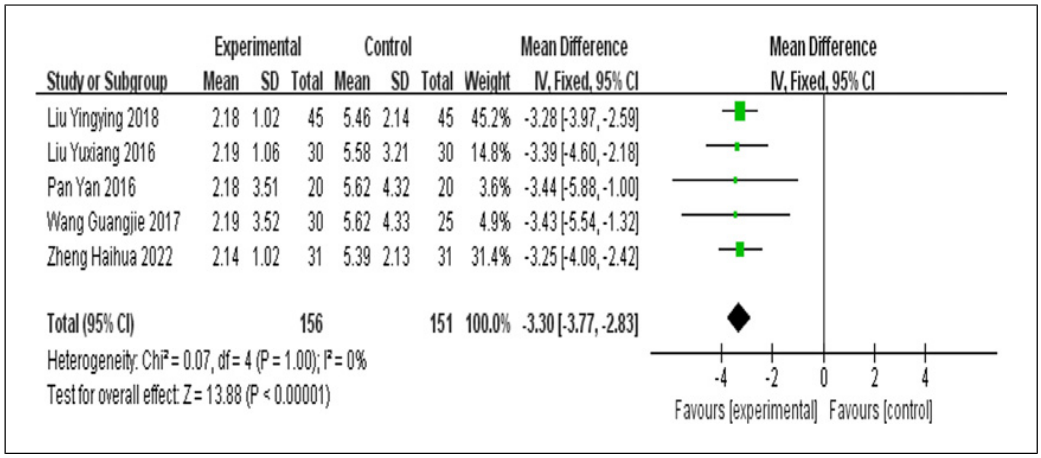

Fig. 7. Comparison of HBO interventions with control in relation to ESS.

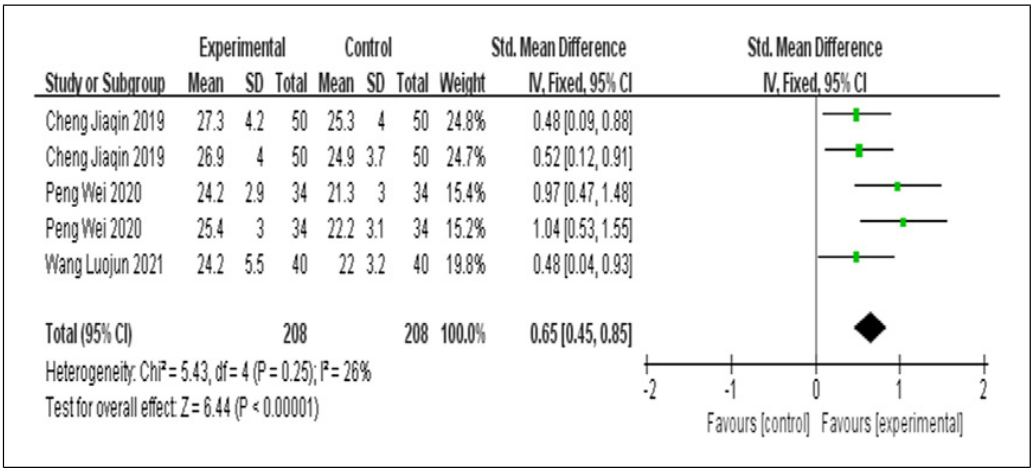

Fig. 8. Comparison of HBO interventions with control in relation to cognitive level.

symptoms and inflammation. Hsu et al. [48] conducted a study on mice using motor activity tests, grip strength tests, and a rotating rod test. They found that after 7 days of HBO treatment, PD mice exhibited increased total walking distance and time on the rotating rod, indicating improved motor ability, muscle endurance, and grip strength. However, there is currently a lack of clinical research on the correlation between peripheral and central inflammation markers and specific motor symptoms such as rigidity, abnormal gait, and balance function in PD. Furthermore, there have been numerous research reports on the relationship between inflammation and non-motor symptoms in PD, suggesting that inflammation may accelerate the progression of depression, anxiety, and fatigue in PD patients [49]. Menza et al. [50] found that serum TNF-α accounted for 25% of the variance in cognitive measures in regression analysis and was closely associated with the results of the Boston Naming Test and Stroop Color Word Test, suggesting that TNF-α may be related to cognitive function in PD patients. Another study using the Hamilton Rating Scale for Depression (HMAD) confirmed a significant positive correlation between serum TNF-α levels and depressive symptoms in PD patients [50]. Sleep disorders are a key factor in reducing the quality of life in PD patients. Animal studies have shown that TNF-α can impair the

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function of biological clock genes and circadian rhythms, leading to excessive daytime sleepiness, fatigue, and increased sensitivity to pain caused by sleep deprivation. Interestingly, HBO therapy can down-regulate pro-inflammatory cytokines while up-regulating anti-inflammatory cytokines in PD patients [51]. Moreover, microglia, as immune cells in the central nervous system, have been shown to rapidly proliferate in the PD pathological process, releasing large amounts of free radicals and causing degeneration of dopaminergic neurons [52]. HBO therapy can reduce this process and inactivate cyclooxygenase. This study also confirmed that under HBO intervention, PD patients exhibited a significant reduction in UPDRS-III motor scores ($p < 0.01$), and excessive daytime sleepiness, excessive daytime sleepiness, and cognitive dysfunction were all alleviated, possibly related to the anti-inflammatory and anti-apoptotic effects of HBO.

The limitations of this study lie in the difficulty of achieving complete blinding in HBO studies, which may affect the reliability of the results of RCT trials to some extent. Additionally, due to the rigorous design requirements, there were only a limited number of eligible studies for analysis, which may also influence the conclusions of this study. Furthermore, there is no consensus on the optimal dosage and duration of HBO therapy, which hampers its application. Therefore, future studies should design and conduct related high-quality, large-sample, multicenter clinical trials to provide more evidence for the effectiveness of HBO therapy in PD.

Conclusion

1. HBO therapy improves the motor symptoms in patients with PD.
2. Sleep disturbance, excessive daytime sleepiness and cognitive dysfunction can be improved by HBO therapy.
3. HBO therapy has the potential to delay the progression of PD due to multiple neuroprotective mechanisms.

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Statement of Ethics

Ethical approval and consent were not required as this study was based on publicly available data.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Shiying Bu: writing – original draft, formal analysis, and visualization. Wuchao Liu: data curation. Xia Sheng: methodology. Lingjing Jin: supervision. Qing Zhao: writing – reviewing and editing and funding acquisition.

Data Availability Statement

The data that support the findings of this study are openly available in (Chinese journal databases CNKI and Wanfang database) at https://www.cnki.net/ and https://www.wanfangdata.com.cn/, reference number [8–20].

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