

BMJ Open Effect of hyperbaric oxygen therapy on cognitive dysfunction induced by nitrous oxide abuse: protocol of a randomised, double-blinded, placebo-controlled trial

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ABSTRACT

Introduction The cognitive dysfunction associated with nitrous oxide abuse is gradually becoming a major global public health concern. Despite the increasing prevalence of nitrous oxide abuse, there are currently no authorised/approved treatment options. Hyperbaric oxygen therapy (HBOT) has been proven to be an efficient method to improve cognitive function. The current randomised, double-blinded, placebo-controlled trial will explore the effect of HBOT on cognitive dysfunction induced by nitrous oxide abuse.

Methods and analysis Eighty participants who abuse nitrous oxide and have cognitive dysfunction, including memory decline, disorientation, attention deficits, slower reactions and learning disabilities, will be included in the trial. They will be randomly assigned to receive either HBOT or sham-HBOT 90–120 min once daily for 5 days per week for 2 weeks. The primary outcome will be the improvement in the total score of the MATRICS Consensus Cognitive Battery, which will measure comprehensive cognitive function between the two groups. Additionally, attention will be measured by integrated visual and auditory continuous performance tests, executive function will be measured by the Wisconsin card sorting test, intelligence will be measured by Raven's standard progressive matrices and cognitive control will be measured by the Stroop colour word interference test.

Ethics and dissemination This protocol was approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee. The report of the study will be disseminated via scientific forums including peer-reviewed publications and presentations at national and international conferences.

Trial registration number Chinese Clinical Trial Registry (ChiCTR2100047111).

INTRODUCTION

Nitrous oxide is a colourless, non-flammable, volatile and inorganic gas with hallucinogenic effects, which is generally referred to as laughing gas. In 1799, it was first reported to have a transient anaesthesia effect and

Strengths and limitations of this study

- This randomised, placebo-controlled, double-blinded trial will provide robust findings on the effect of hyperbaric oxygen therapy (HBOT) in patients with cognitive dysfunction caused by recreational nitrous oxide use, which has rarely been investigated thus far.
- Cognitive function will be assessed by the MATRICS Consensus Cognitive Battery, integrated visual and auditory continuous performance test, Wisconsin card sorting test, standard progressive matrices and colour word interference test and will provide valuable insights into alterations in the different dimensions of cognitive function.
- The generalisation and application of the results of this single-centre study to a broader population may be limited.
- The findings from the 10 applied exposures of HBOT will be novel but will not provide enough evidence to directly implement long-term HBOT for patients with cognitive dysfunction caused by recreational nitrous oxide use.
- We will not have follow-up evaluations of cognitive dysfunction, so the further effect of HBOT will be unknown.

cause powerful euphoria.^{1 2} During the 19th century, it was prevalent in theatre halls where actors commonly used it as a recreational gas to relieve pain during the performance. The recreational use of nitrous oxide became popular again in the 1960s, and it was used as a recreational drug worldwide via a variety of methods, such as inhalation through canisters, balloons and respirator-tight bags.² According to the 2018 Global Drug Survey that included more than 115 000 participants, the percentage of participants with lifetime use of nitrous oxide was 16.0%, and that of participants with past 1 year use

was 7.7%.³ The percentage of participants using nitrous oxide in England and Wales was 2.2% in those aged 16–59 years (n=763 000) from 2018 to 2019. The number was 8.7% among participants aged 16–24 years, and nitrous oxide was the second most popular recreational drug in the region after cannabis (17.3%).⁴ In 2019, a survey from the National Ecstasy and Related Drugs Reporting System in Australia that included 797 participants (60% male) with an average age of 22 years showed that the percentage of use of nitrous oxide in the past 6 months was 53%, which was two times higher than the 26% reported in 2003.⁵ Although there was no official information on the recreational use of nitrous oxide in China, a report released by the Narcotic Control Products Committee in 2017 mentioned that new psychoactive substances, such as nitrous oxide, have emerged in recent years.⁶ A recently published review reported that nitrous oxide abuse showed a rising trend in China, with the resulting problems becoming more serious and demanding further research to improve measures of prevention, treatment and rehabilitation.⁷

Long-term and high-dose nitrous oxide use can cause vitamin B₁₂ deficiency, which is related to peripheral nerve impairment and megaloblastic anaemia.² Nitrous oxide inhalation can also cause frostbite in the oral cavity and upper aerodigestive tract.⁸ Moreover, exhalation of the inhaled gas into a balloon to seek stimulation can easily lead to hypoxia and asphyxia. Nitrous oxide itself does not cause severe respiratory inhibition, but it prevents the physiological response to hypoxia at high concentrations (50%).² The study reported that memory impairment, learning difficulties and psychomotor activity were reduced with subanaesthetic concentrations of nitrous oxide.⁹ Dreyfus *et al* reported the development of chronic toxic encephalopathy with cognitive decline as a result of chronic exposure to nitrous oxide in two anaesthetists who constantly worked in an operating room. They presented deficits in attention, executive functioning, short-term memory and visuospatial organisation, and the symptoms slowly improved after the cessation of occupational exposure and treatment with antidepressants and neuropsychology.¹⁰ In addition, recent cases also reported that nitrous oxide abuse may cause cognitive dysfunction;^{11 12} however, the characteristics of cognitive impairment due to nitrous oxide abuse are unknown.

Hyperbaric oxygen therapy (HBOT) is widely used to treat hypoxic and ischaemic diseases, such as stroke and carbon monoxide poisoning. Patients were asked to inhale 100% oxygen in an environment above an absolute atmospheric pressure of one to increase tissue oxygenation during the treatment. Previous studies found that HBOT can improve blood oxygenation, induce stem cell proliferation and angiogenesis,^{13 14} increase the number of cholinergic neurons in the hippocampus and enhance learning and memory.¹⁵ Therefore, HBOT may be a safe, effective and non-invasive treatment for improving cognitive function. However, the effect of HBOT on the cognitive dysfunction induced by nitrous oxide abuse is

unknown. We previously reported the improvement of cognitive function with HBOT in a patient who abused nitrous oxide.¹¹ Based on this finding and the literature regarding the improvement of cognitive function with HBOT, we plan to conduct a randomised, double-blinded, placebo-controlled trial to investigate the effect of HBOT on cognitive dysfunction in patients who abuse nitrous oxide.

METHODS AND ANALYSIS

Study objective and hypotheses

The objective of this study is to investigate the effect of HBOT on cognitive dysfunction induced by nitrous oxide abuse. Cognitive dysfunction includes comprehensive cognitive function, attention, executive function, intelligence and cognitive control. We hypothesise that HBOT will improve comprehensive cognitive function as measured by the MATRICS Consensus Cognitive Battery (MCCB) as well as attention, executive function, intelligence and cognitive control.

Study design

The study will be a randomised, double-blinded, placebo-controlled trial to evaluate the effect of HBOT on cognitive dysfunction. Participants will receive a cognitive assessment at baseline and be randomised with a 1:1 allocation to the treatment group or control group. The treatment group will receive general and HBOT treatments, and the control group will receive general and sham-HBOT treatments (the participant will go into the chamber but will not actually receive an inspired oxygen pressure of >1.4ATA). General treatment will include supplying vitamins. The flow chart of the trial is presented in figure 1. Examinations will be carried out in the West China Hospital of Sichuan University, Chengdu, China, from spring until winter 2022. The protocol was approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee (Version 2.0) and written informed consent will be obtained from all participants by the investigator.

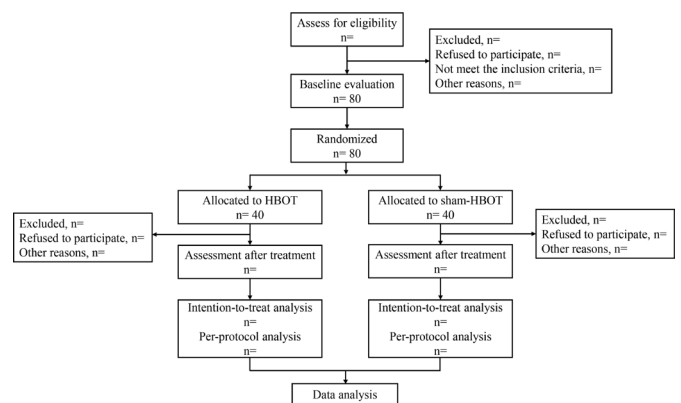


Figure 1 Consolidated Standards of Reporting Trials flowchart of the trial. HBOT, hyperbaric oxygen therapy.

Eligibility and recruitment

Participants aged 18–60 years, with a history of nitrous oxide exposure, who meet the diagnostic criteria for substance abuse in the DSM-5 and with acute, subacute or chronic symptoms of cognitive dysfunction (eg, memory decline, disorientation, attention deficits, slower reactions and learning disabilities) as evaluated by an experienced psychiatrist will be included. The exclusion criteria include participants with brain diseases (eg, intracerebral haemorrhage, cerebral infarction), psychoactive substance abuse (alcohol, tobacco, opioids, ecstasy, caffeine abuse and so on), HBOT contraindications and other causes of cognitive decline.

Social media and advertisements will be used in the recruitment of participants. Recruitment will be carried out in the Mental Health Center of West China Hospital, Sichuan University, Chengdu, China. The hospital is a pre-eminent public hospital in the western part of China. The Mental Health Center is one of the four major mental health centres in China, with patients from all over the country. Patients with a history of nitrous oxide abuse will be screened, and those meeting the inclusion and exclusion criteria will be invited to participate in the study. A face-to-face interview will be arranged by an experienced investigator for those who are interested in the trial. The details of the study's purpose, methods, benefits and possible discomfort or risks will be provided to the subjects and their guardians; if the subjects understand the information, they will sign the informed consent form; if the subjects have a poor capacity to provide consent, consent will be given by their guardians (online supplemental file). The participants will not be involved in the recruitment and conduct of the study.

Sample size calculation

The minimal clinically important difference in the MCCB score is assumed to be 5 (SD 10) based on a previous study.¹⁶ To detect these differences with a 2-sided significance level of 0.05% and 80% power, a total sample size of 68 participants will be needed. Therefore, the aim of this study will be to recruit 80 participants to account for potential dropouts.

Randomisation and interventions

The participants will be randomised in balanced blocks of eight and assigned to sequences of treatment by choosing a sealed envelope with allocations of HBOT or sham-HBOT, conducted by an investigator who is not involved in preparing the sealed envelope. The participants in the active treatment group will breathe 100% oxygen at 2.0 atmospheres of absolute pressure (ATA), and participants randomised to the placebo group will breathe 21% oxygen at 1.2 ATA.¹⁷ Both groups will receive 90–120 min of air pressure exposure once daily for 5 days per week for 2 weeks (total of 10 exposures). All the participants will complete a form about adverse effects after each treatment every day. Additionally, all the participants will receive general treatment, including the supply of

vitamins, according to the symptoms or severity of the disease.

Participants who are not willing to continue with the therapy, are re-exposed to nitrous oxide during the therapy and are unable to tolerate the adverse effects of HBOT (headache, dizziness, vomiting, tinnitus and so on) will discontinue the therapy after evaluation by the chief investigators. Those who have severe adverse effects, such as sudden deafness, hearing loss, external auditory canal haemorrhage, pulmonary barotrauma and oxygen poisoning, will stop the therapy immediately and receive the corresponding treatment. The participants with severe adverse effects will have follow-up screening every week in the first month and every 2 weeks in the following 2 months. The participants who discontinue the trial will also complete the cognitive function assessment.

Blinding

All participants, researchers and the person who performed the data analysis will be blinded to the order of the therapy. An independent technician who is not aware of the study protocol will perform HBOT and sham-HBOT. Unblinding is permissible if a participant quits the trial or experiences severe adverse effects. The independent technician will reveal the allocation intervention of the participant.

Assessments

Clinical assessment

Demographic and clinical data will be obtained from all participants, including age, sex, education level, marital status, age at onset of nitrous oxide use and duration of use, amount and frequency of nitrous oxide exposure, clinical signs and symptoms, alcohol-drinking history (frequency of alcohol drinking and the average amount of alcohol consumed on a drinking day), smoking history (frequency of smoking and number of cigarettes per day), abuse of other substances and family history of psychiatric disorders.

Cognitive function assessment

To maintain validity, neurocognitive testing will be gauged by an independent person.

Schizophrenia cognitive functioning battery consensus version (MCCB)

The Chinese version of the MCCB will be used to assess cognitive performance. This is a package of 10 tests including 7 cognitive domains, such as processing speed (semantic fluency, linking test and symbolic coding), attention/vigilance (the continuous operations test), working memory (number sequences and spatial breadth), verbal learning (the revised Hopkins verbal learning test), visual learning (a modified version of the brief visual memory test), reasoning and problem solving (the maze test) and social cognition (the emotional management test). The raw scores and normalised scale scores will be recorded, and a higher score will indicate better cognition.¹⁸

Integrated visual and auditory continuous performance test

The integrated visual and auditory continuous performance test (IVA-CPT) consists of the visual continuous performance test (VCPT) and auditory continuous performance test (ACPT). In the VCPT, numbers 0–9 will appear randomly on the screen for 200 ms with interstimulus intervals of 1300 ms. The participants will be asked to press the space button when they see the number ‘3’. The total test time is 12 min, and the target character is 96, accounting for 20% of the total number of 480. In the ACPT, the computer randomly reports aural stimuli from 0 to 9, each with interstimulus intervals of 1500 ms. The participants will be asked to press the space button after hearing the number ‘3’. The total test time is 12 min, and the target number accounts for 10% of the total number of characters. The number of false errors, missed errors and average response time will be automatically recorded in both tests and converted to standard values (T values). The higher the standard value, the more severe the impairment of attention.¹⁹

Wisconsin card sorting test

The Wisconsin card sorting test (WCST) is a method to assess executive function, such as set shifting, concept formation and problem solving, in response to tester feedback. The test consists of 6 classifications and a total of 128 cards. According to the tester’s rule, the participants will be asked to choose one card from the four stimulus cards that best matches the response card.²⁰

Raven’s standard progressive matrices

Raven’s standard progressive matrices (SPM) is a non-verbal intelligence test that requires subjects to fill in the gaps in a large figure with an appropriate answer based on the symbols or patterns in the figure. The Chinese version includes 60 questions, divided into 5 groups of 12 questions each. One point is recorded for each correct answer. The higher the score, the better the performance. The raw scores will be transformed into scale scores through the age normative scale to assess the intelligence levels of the subjects.

Stroop colour word interference test

The Stroop colour word interference test (CWT) is a test to evaluate cognitive control that consists of three steps. In the first step, the participants will be asked to read the words (yellow, red, blue and green) on card A as quickly and correctly as possible. In the second step, the participants will be asked to read the colour of the dots on card B as quickly and correctly as possible. In the third step, the participants will be asked to read the colour, but not the meaning, of the words on card C as quickly and correctly as possible. The Stroop interference effects (SIE) are measured as follows: SIE time consumption= time consumption of card C–time consumption of card B; and SIE correct=correct number of card C–correct number of card B. The larger the SIE is, the lower the effectiveness of interference suppression.

Outcome assessment

The primary outcome will be the difference in the total score of the MCCB, which measures the comprehensive cognitive function between the two groups. The secondary outcomes will include the differences in the value of the IVA-CPT, WCST and SPM and the SIE of the CWT.

Statistical considerations and data management

The statistical analysis will be conducted using SPSS V.24. Continuous variables will be presented as the mean±SD, and categorical variables will be presented as counts and percentages. The MCCB score (primary outcome) will be analysed by the intention-to-treat principle, including the data from all randomised participants. A per-protocol analysis of other parameters from the participants who complete the whole study will also be performed. Missing data will be replaced by multiple imputations using multivariable regression models with chained equations. Another option for dealing with missing data will be the replacement of missing data by the corresponding data from the opposite treatment, which assumes no treatment effect. The mean treatment differences and 95% CIs between measures with HBOT and sham-HBOT will be computed. All statistical tests will be two-sided, and the statistical significance will be set at $p<0.05$.

Once collected, data will be deidentified, and a study ID will be developed for each participant. Only authorised researchers will have access to the data. Furthermore, a variety of security controls will be implemented. Given the short period of the intervention and low risk of the trial, a data monitoring committee will not be formed. However, regular data review will be performed to minimise adverse events and other unintended effects.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research. We plan to disseminate the results of the study to the trial participants via their indicated preferred method of contact, which will be a part of the information that is collected at their initial appointment with the psychiatrist.

Ethics and dissemination

The protocol was approved by the West China Hospital of Sichuan University Biomedical Research Ethics Committee. The report of the study will be disseminated via scientific forums, including peer-reviewed publications and presentations at national and international conferences.

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