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Ozone therapy for long COVID

Submission date
19/10/2025

Recruitment status
No longer recruiting

Registration date
23/10/2025

Overall study status
Completed

Last Edited
23/10/2025

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Ozone therapy in medicine is an increasingly popular treatment for various conditions involving redox imbalance, chronic hypoxia, inflammation, and immune deficiencies. It consists of the administration of ozone, mainly through two routes: indirect intravenous (or autohemotherapy) and rectal insufflation. In rectal insufflation, a gas enema is administered that will react with the intestinal mucus, generating peroxides and other molecules that will pass into the general venous circulation through the hemorrhoidal plexus. Controlled oxidative stress is induced, producing antioxidant, anti-inflammatory, and immune improvements. This technique is well-tolerated and very safe. Absolute contraindications include pregnancy and severe glucose-6-phosphate dehydrogenase deficiency (favism), due to the risk of hemolysis. The technique has been used successfully and safely in both COVID-19 and fibromyalgia, a condition with clinical features like those of persistent COVID. A review of 13 clinical studies on the treatment of COVID-19 with medical ozone (271 patients in total) showed good tolerability and clinical, functional, analytical, and radiological improvements. Given the need for treatment in patients affected by persistent COVID and considering the clinical similarity between this disease and fibromyalgia, this study proposes to replicate a successful study previously conducted by this team, which demonstrated the efficacy and good tolerability of rectal ozone therapy in COVID-19.

Who can participate?
Adult patients with persistent COVID

What does the study involve?
Participants will be treated with 24 ozone therapy sessions over a period of 12 weeks.
During the first visit, inclusion and exclusion criteria will be checked, and the patient's informed consent will be obtained.
At the second visit, treatment with systemic ozone therapy via the rectal route (8 mg; 200 ml of gas at a concentration of 40 mcg/ml) will be initiated. Sessions will take place five days a week for the first 2 weeks, two days a week from week 3 to week 6, and one day a week from week 7 to week 12.
Each patient will undergo a baseline thermographic study before the first rectal application, as well as weekly recordings, up to 15 days and one month after the end of treatment.
The main variables (PCFS, FSS, and SF-12) will be recorded every 15 days from the start of treatment, and 15 days and one month after completion of treatment.

Adverse effects will be recorded at each medical ozone application visit, and the PGIs and PGIi scales will be collected weekly. The other variables will only be recorded at baseline, before starting treatment, and fifteen days after the last medical ozone treatment session.

What are the possible benefits and risks of participating?
The effect of ozone can cause a reduction in systemic inflammation, an improvement in quality of life, and a decrease in levels of fatigue, concentration, pain, and mood.
Adverse effects that have been reported include flatulence and mild, temporary abdominal and intestinal discomfort.

Where is the study run from?
Universidad Católica de Murcia, Murcia, Spain.

When is the study starting and how long is it expected to run for?
September 2024 to April 2026. The study enrolment will last for three months, from November 2025 to January 2026

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
Alessio Cabizosu, acabizosu@ucam.edu

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Protocol serial number
TC/1924

Study information

Scientific Title

Efficacy and tolerability of ozone therapy in persistent COVID. Clinical and physiological study

Acronym
Long-Covid-Ozone

Study objectives
Describe the efficacy and tolerability of ozone therapy in patients with persistent COVID-19.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 27/09/2024, Universidad Catolina San Antonio (UCAM) Ethics Committee (Av. de los Jerónimos, 135,, Guadalupe de Maciascoque, Murcia, 30107, Spain; +34 968 278 828; comite_etica@ucam.edu), ref: CE092407

Study design
Interventional non-randomized study

Primary study design
Interventional

Study type(s)
Diagnostic, Efficacy, Quality of life, Safety, Treatment

Health condition(s) or problem(s) studied
Chronic fatigue, quality of life, and pain in patients with persistent COVID-19.

Interventions
As for the ozone protocol, 8 mg of medical ozone (200 ml of gas at a concentration of 40 µg/ml) will be administered per session. The complete protocol will consist of 24 sessions of rectal ozone therapy over a period of 12 weeks. The insufflation power of the device will be calibrated to 100-240 V / 50-60 Hz, with an insufflation rate of 1.0 l/min. Five sessions per week will be administered during the first two weeks, two sessions per week from week 3 to week 6, and one session per week from week 7 to week 12.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Rectal ozone gas

Primary outcome(s)
The following primary outcome measures are assessed throughout the study at the beginning of each week:
1. Functional limitations when subjects carry out their tasks and activities of daily living, as well as changes in their lifestyles, are measured using the Post-COVID-19 Functional Status Scale (PCFS)

2. Incapacitating fatigue is measured using the Fatigue Severity Scale (FSS)
3. Cognitive screening is measured using the Montreal Cognitive Assessment Test (MoCA)
4. The intensity of pain (sensory dimension), as well as the interference of pain in the patient's life (reactive dimension), is measured using the Brief Pain Inventory (BPI)
5. Headache impact is measured using the Headache Impact Test (HIT-6)
6. Overall health status in terms of physical, social, and emotional aspects, vitality, and pain is measured using the Short-Form Health Survey (SF-12)
7. Hand grip strength is measured using the Handgrip Strength Test (HST)
8. The overall clinical impression of disease severity is measured with Patient Clinical Global Impression Severity (PGIs)
9. The overall clinical impression of improvement, as assessed by the patient, is measured with Patient Clinical Global Impression Improvement (PGIi)

Key secondary outcome(s))
The following secondary outcome measures are assessed throughout the study at the beginning of each week:
1. Depression is measured using the Beck Depression Inventory Second Edition (BDI-II)
2. The presence and severity of anxiety, as well as the individual's propensity to suffer from it, are measured using the State-Trait Anxiety Inventory (STAI)
3. Sleep Quality is measured using the Pittsburgh Sleep Quality Inventory (PSQI)

Completion date
01/04/2026

Eligibility

Key inclusion criteria
1. Patients aged between 18 and 70 years old with a confirmed diagnosis of persistent COVID
2. Positive swab test for SARS-CoV2 infection
3. Patients who sign an informed consent form to participate in the study
4. Patients capable of understanding and performing the tasks for the proposed tests
5. Patients who are able to participate in the study for a period of 12 weeks

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
70 years

Sex
All

Key exclusion criteria
1. Patients suffering from any psychiatric disorder specified in axis I of the DSM-V other than major depression
2. Patients with a history or current history of substance abuse. Those patients with a history of substance use will be admitted if they have been abstinent for at least one year
3. Patients with a history or current history of substance abuse. Those patients with a history of substance abuse will be admitted if they have been abstinent for at least one year
4. Patients who are unable to clearly understand the objectives and methodology of the study
5. Pregnant or breastfeeding women
6. Patients with hyperthyroidism
7. Pregnant or breastfeeding women
8. Patients with hyperthyroidism
9. Patients with favism
10. Subjects who report in advance that they will be unable to attend all the required ozone therapy sessions
11. Patients who have been treated with medical ozone in the 9 months prior to the start of treatment

Date of first enrolment
01/11/2025

Date of final enrolment
01/02/2026

Locations

Countries of recruitment
Spain

Study participating centre
Clinalgia SL
Av. de la Libertad, 3,
Murcia
Spain
30009

Sponsor information

Organisation
Universidad Católica de Murcia

ROR
https://ror.org/05b1rsv17

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analyzed during the current study will be available upon request from: acabizosu@ucam.edu

IPD sharing plan summary
Available on request