

# Whole-Body Cryotherapy as an Innovative Treatment for COVID 19-Induced Anosmia-Hyposmia: A Feasibility Study

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## Abstract

**Objective:** This study assessed the impact of two different doses of whole-body cryotherapy (WBC) on smelling capacities of COVID-19 recovered French patients with persistent anosmia or hyposmia.

**Methods:** A pilot randomized controlled trial was conducted by using a convenience sample of 45 hyposmic/anosmic patients (32 female, 13 male, mean age [standard deviation]: 39.5 [14.7] years). The severity of olfactory deficits was examined by using a visual analogue scale (VAS) at baseline, post-intervention, and follow-up (1 week). Patients were randomly allocated to either control (no intervention,  $n=15$ ) or one of the two treatment groups (“low-dose” WBC, 2 days,  $n=15$ ; “high-dose” WBC, 5 days,  $n=15$ ) via block randomization by using baseline anosmia as strata. A mixed-design analysis of variance with group (“control,” “low-dose” WBC, “high-dose” WBC) as between-subject variable and time points (baseline, post-intervention, follow-up) as within-subject variable was conducted, followed by *post hoc* analysis for significant or interaction effects.

**Results:** The WBC appeared to be safe, and no adverse effects were observed. A significant group by time interaction effect was observed. Although no differences between groups were found at pre- and post-intervention, significant differences were found at follow-up in favor of the high-dose group only. The magnitude of difference in the VAS anosmia score was found to be of large size compared with patients in the control and low-dose groups (Hedges’ corrected effect size of 0.96 and 1.04 respectively). Within-group comparisons revealed significant improvements in smelling capacities from pre- to post-intervention, and then again from post-intervention to follow-up in both WBC groups. However, the magnitude of change was less pronounced in patients who received the low-dose WBC intervention.

**Conclusion:** The WBC might be beneficial and safe for patients with severe acute respiratory syndrome coronavirus-2-induced olfactory dysfunction; however, further research is necessary to confirm the findings of this pilot study, and to investigate the mode of action.

**Keywords:** COVID 19-induced anosmia-hyposmia, whole-body cryotherapy, randomized controlled trial

## Introduction

**O**LFACTORY DYSFUNCTION (OD) in the form of anosmia or hyposmia is a particularly prominent symptom in COVID-19 patients, with an incidence rate ranging from 34%

to 68%, and a female predominance.<sup>1–3</sup> Paderno and colleagues<sup>4</sup> even demonstrated that OD occurred as the first symptoms in 10% of COVID-19 cases.

Although spontaneously resolved in the majority of cases after within 2–4 weeks,<sup>4</sup> research indicates that up to 50.7%

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of individuals may have persisting OD at up to 40 days from the onset of COVID-19.<sup>6</sup> In addition, some studies describe that the percentage of patients with OD at 60 days varies between 15.3%<sup>7</sup> and 32.6%,<sup>8</sup> causing a profound effect on quality of life.<sup>5</sup>

Though the underlying pathogenic mechanisms in COVID-19 anosmia are still debated, the local inflammation in the nasal cavity is thought to play a pivotal role in causing olfactory loss.<sup>9,10</sup> One hypothesis is that the virus enters the central nervous system through the first neurons of the olfactory pathway, also called olfactory sensory neurons, located in the olfactory mucosa. The olfactory mucosa is a specialized neuroepithelium located in the highest portion of the nasal cavity in direct contact with the external environment below the cribriform plate.

Then, the virus crosses the cribriform plate to reach the olfactory bulbs, which contain the second olfactory neurons.<sup>11</sup> There is preliminary empirical support for this hypothesis, with recent magnetic resonance imaging (MRI) studies showing olfactory bulb inflammation in COVID-19 patients with OD.<sup>12,13</sup>

Another hypothesis states that anosmia results from damage to supporting sustentacular cells (i.e., the supporting cells surrounding the olfactory neurons) rather than to olfactory sensory neurons, which suggests that the resulting inflammatory milieu, rather than the direct neuronal damage, is disease-causing.<sup>14</sup> Inflammation of the olfactory clefts in patients with post-COVID OD has been demonstrated from studies using MRI scans,<sup>15</sup> supporting an inflammatory pathophysiological mechanism.

Olfactory training combined with oral steroids has demonstrated efficacy in preliminary studies that included COVID-19 patients with persistent olfactory deficits.<sup>16</sup> However, given the well-known side effects of systemic steroids, alternatives with a low risk of side effects are highly needed.

In the past 10 years, whole-body cryotherapy (WBC) has been documented to be an effective add-on treatment for various neuroinflammatory diseases.<sup>17</sup> Immunomodulation is a potential mediating mechanism through which WBC exerts its therapeutic benefits. For instance, several studies highlighted that exposure to extremely low temperatures leads to a decrease in oxidative stress and reduces the inflammatory response.<sup>18</sup>

Using a randomized controlled trial design, this study evaluated the impact of two different doses of WBC on the smelling capacities of former COVID-19 French patients. The first intervention required patients to take two sessions of WBC over one working week. The second, more radical, intervention involved taking daily sessions of WBC over one working week (five consecutive WBC sessions).

## Methods

Because there have been no other studies that have investigated the use of WBC for COVID-19 patients suffering from persistent anosmia or hyposmia, an effect size estimate for our primary outcome is not known, which made it impossible to determine an *a priori* minimum sample size to secure a study power of 0.80 and an  $\alpha$  value of 0.05. However, since the goal of this feasibility study was also to estimate an effect size, our sample size considerations were

based on the recommended sample sizes of at least 40 when estimating the pooled standard deviation (SD) of any continuous outcome.<sup>19</sup>

Having secured University ethics clearance, a convenience sample of 32 women (mean age = 38, SD = 13 years) and 13 men (mean age = 42, SD = 16 years) with persistent anosmia or hyposmia after diagnosis of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (positive reverse transcription polymerase chain reaction test) volunteered to be involved and completed informed consent. All patients complained of persistent anosmia-hyposmia that occurred after COVID-19 infection. Eighteen percent of patients presented anosmia or hyposmia without any other symptoms.

Among the remaining participants, dysgeusia (67%), fever (55%), dyspnea (34%), and fatigue (4%) were the four main co-symptoms. Pre-intervention smelling capacities were assessed by using the subjective visual analogue scale (VAS) olfactory assessments (0–100), with “0” = complete loss of smell and “100” = normal smelling ability. Finally, participants were examined by a physician who confirmed that they had no history of ODs or respiratory tract symptoms before COVID-19 diagnosis, and that they had no medical contraindications to WBC.

After pre-intervention testing, participants were randomly and equally assigned, via block stratification by using baseline anosmia as strata. The three subjects having the highest anosmia score were randomly assigned to one of the three groups (“control”; “low-dose WBC”; “high-dose WBC”) by one investigator not involved in the selection or treatment of the subjects. The allocation sequence was generated by a computer in the form of a random number table with three code groups (1 for “control,” 2 for “low-dose,” and 3 for “high-dose”). This procedure of blocking and random assignment continued with the next block of three highest anosmia subjects, and so on and so forth, until all subjects were placed in a group.

During WBC sessions, participants were exposed to extremely low temperatures (−60°C to −110°C) in a double Cryoair chamber (MECOTEC, Pforzheim, Germany) for 3 min. They entered a vestibule chamber at −60°C where they stayed for about 30 sec of body adaptation before passing to a cryochamber at −110°C where they had to remain for 2 min ½. All subjects were minimally dressed: bathing suit, socks, clogs, headband, and surgical mask to avoid direct inhalation of cold air. Participants in the two WBC groups received detailed guidance on what actions to take in case of adverse events.

Smelling capacities were assessed at three points (pre-intervention, post-intervention, 1 week follow-up) by using self-reported VAS olfactory assessments (0–100), with “0” = complete loss of smell and “100” = normal smelling ability.

Consistent with CONSORT recommendations for analyzing randomized controlled trial designs, the magnitude of difference between pre-intervention and post-intervention, and then between pre-intervention and follow-up data were compared between groups to identify intervention effects. Consequently, a mixed-design analysis of variance (ANOVA) was used with group (“control,” “low-dose” WBC, “high-dose” WBC) as between-subject variable and time points (pre-intervention, post-intervention, follow-up) as within-subject variable.

In case of significant main or interaction effects, *post hoc* tests were conducted to examine the effects, including one-way ANOVA, or *t* tests. For all analyses, the significance level was set at 5% ( $p \leq 0.05$ ), as usual. Finally, Cohen's *ds* were used to indicate the magnitude of differences (effect size) between each of the two WBC groups in comparison to the control group. We used Hedges' correction to adjust *d* for small sample size. Cohen<sup>19</sup> describes *d* values as 0.2 being small, 0.5 as medium, and 0.8 as large effect sizes. All analyses were performed by using JASP (version 0.14.1). The data that support the findings of this study are available on request from the corresponding author.

## Results

The total sample was 45 participants, and all participants provided data at each time point. No adverse effect was reported in patients from the two WBC groups. The CONSORT flowchart of participants is presented in Figure 1.

Results of the mixed-design ANOVA (between-subject variable: group; within-subject variable: time points) indicated a significant group  $\times$  time interaction,  $F(4, 84) = 17.36$ ,  $p < 0.001$ . Age, sex and months of olfactory deficits as covariates did not change the results. *Post hoc* one-way ANOVAs revealed no significant differences in the mean score of anosmia between the three groups at baseline and post-intervention.

However, 1 week later (at follow-up), participants in the "high-dose" WBC group reported significantly higher VAS scores (namely, less olfactory impairment) than participants in the "control" group [ $t(28) = 2.66$ , Bonferroni-adjusted  $p$ -value = 0.030, Hedges' corrected effect size = 0.96] and than those in the "low-dose" WBC group [ $t(28) = 2.74$ , Bonferroni-adjusted  $p$ -value = 0.027, Hedges' corrected effect size = 1.04].

Examination of within-group changes revealed that in participants from the "low-dose" WBC group, the mean VAS score significantly improved from pre- to post-intervention (Hedges' corrected effect size = 1.11), and then again from post-intervention to follow-up, although by a more moderate rate (Hedges' corrected effect size = 0.59). These findings were seen in the participants from the "high-dose" WBC group as well, with even larger effect sizes (Hedges' corrected effect size of 1.56 and 0.99 respectively).

No significant within-group change in self-rated anosmia was noted for participants in the control group. Table 1 shows the mean values of VAS scores according to group and time point.

## Discussion

What we report here are the results of a feasibility pilot study evaluating the effects of repeated whole-body cold

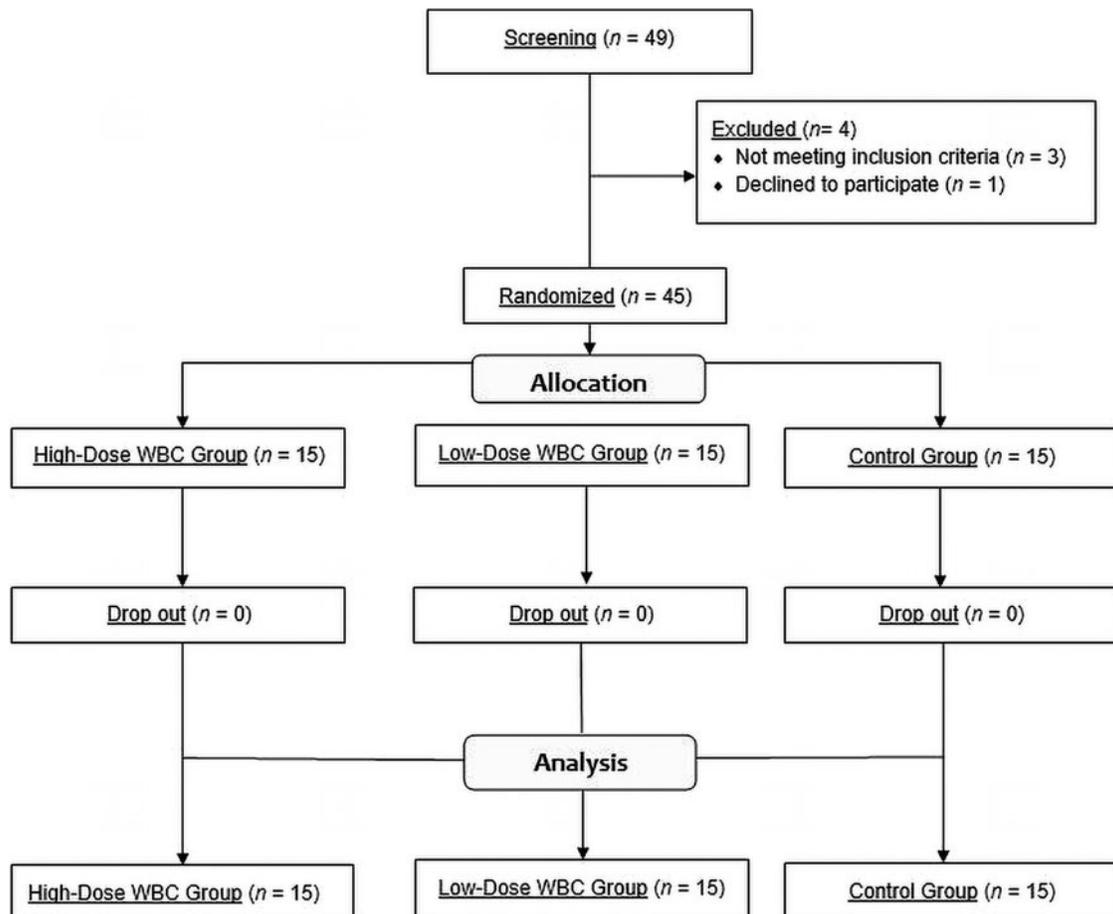


FIG. 1. Flowchart of study participants through the trial. WBC, whole-body cryotherapy.

TABLE 1. MEAN VISUAL ANALOGUE SCALE SCORE FOR THE THREE EXPERIMENTAL GROUPS AT EACH TIME POINT, AND GROUP DIFFERENCES AT POST-INTERVENTION AND FOLLOW-UP

|                                  | <i>Pre-intervention</i> | <i>Post-intervention</i> | <i>Follow-up</i>        |
|----------------------------------|-------------------------|--------------------------|-------------------------|
| VAS score, mean (SD)             |                         |                          |                         |
| Control ( <i>n</i> = 15)         | 32.40 (27.23)           | 33.40 (27.60)            | 34.40 (27.21)           |
| Low-dose WBC ( <i>n</i> = 15)    | 25.33 (21.91)           | 31.80 (25.64)            | 33.67 (25.11)           |
| High-dose WBC ( <i>n</i> = 15)   | 32.80 (20.44)           | 47.33 (23.67)            | 58.00 (19.98)           |
| Group differences, mean [95% CI] |                         |                          |                         |
| Control vs. low-dose WBC         |                         | −1.60 [−24.99 to 22.79]  | −0.73 [−22.85 to 21.38] |
| Control vs. high-dose WBC        |                         | 13.93 [−9.46 to 37.32]   | 23.60 [1.48 to 45.72]   |
| Low-dose WBC vs. high-dose WBC   |                         | 15.53 [−7.86 to 38.92]   | 24.33 [2.22 to 46.45]   |

CI, confidence interval; SD, standard deviation; VAS, visual analogue scale; WBC, whole-body cryotherapy.

exposure for adults with COVID-19-induced olfactory deficits. The WBC was well received by patients of both genders as testified by the particularly high values of adherence rates (100%), and no reports of adverse effects.

Our brief recruitment period, 1 month in duration, suggests that many patients who wanted to participate could not enter the study because of the short amount of time available to make a decision and initiate action (obtaining a medical clearance for WBC, making time slots vacant for WBC sessions, etc.). In addition, there were significant scheduling restrictions since WBC sessions were offered only on specific dates, which sometimes led to time and scope constraints on other activities. This indicates that the ease of access to the WBC program and schedule flexibility are critical for delivering such a treatment.

Our pre-intervention, post-intervention, and follow-up assessments reveal that WBC could lead to clinically meaningful improvements in self-reported smelling capacities (+25 points on a 0–100 VAS). In summary, our pilot study supports the feasibility and potential utility of WBC in at least a subset of patients with COVID-induced persistent anosmia or hyposmia.

Importantly, the benefits of WBC appeared rapidly (1 week), which is highly valuable given that pharmacologic treatments for postviral OD usually take >4 weeks to show any results.<sup>21</sup> The WBC has been demonstrated to trigger anti-inflammatory actions quite quickly, which could explain our encouraging results.<sup>22</sup> In support of this suggestion, findings by Lubkovska and colleagues<sup>22</sup> highlighted that exposure to extremely low temperatures leads to a rapid decrease in the concentration of pro-inflammatory cytokines interleukin 1 $\alpha$  (IL-1 $\alpha$ ), and a rapid increase in anti-inflammatory cytokines interleukin 10 (IL-10).

Our study results must be viewed in light of some limitations. First, self-report assessment of smelling capacity directly after the intervention may have been flawed as the participants were not in their natural environment when completing the post-intervention VAS. Rather than being the result of increased anti-inflammatory cytokines and/or decreased pro-inflammatory cytokines, the immediate post-intervention changes in smelling capacity could be explained by reactive increased blood flow in the nasal mucosa, or still other unknown factors.

Second, no blinding of participants was used, which could have influenced the results. A placebo approach will be needed in future studies. Third, this was only a pilot study, so factors other than age, sex, and baseline anosmia scores

were not considered as potential confounders. Still another limitation is that no objective biomarkers (e.g., pro-inflammatory and/or anti-inflammatory interleukins) were collected alongside self-reported VAS scores.

Exclusive reliance on self-report is a very sensitive issue, as it is affected by respondents' mental access to requested information. Consequently, replication of the present study using external measurements of smelling capacities (e.g., Sniffin' Sticks olfactory tests) is highly needed. Finally, our study sample was atypical in that the majority of our participants were female from medium to high socioeconomic status.

Of note, the medical literature suggests that female gender and high socioeconomic status are factors associated with complementary and alternative medicine use among the general population,<sup>23</sup> and these factors may have also influenced our study sample. Men were clearly not attracted toward this feasibility study, and future work will have to explore gender-specific recruitment and intervention effects.

## Conclusion

In this pilot study, gains in olfactory function were clinically important in anosmic or hyposmic patients who received high-dose WBC (5 sessions over 1 week), with improvements  $\geq 50\%$  when comparing pre-intervention with follow-up assessments. We conclude that WBC might be beneficial and safe for patients with SARS-CoV-2-induced OD; however, further research is necessary to confirm the findings of this pilot study, and to investigate the mode of action.

## Authors' Contributions

All coauthors have reviewed and approved the article before submission. Coauthors' contributions are stated next. B.B. had full access to all the data in the study and takes responsibility for the integrity of the data, and G.P. takes responsibility for the accuracy of the data analysis. Concept and design: E.B., F.D.L., and G.P. Acquisition, analysis, or interpretation of data: All authors. Drafting of the article: G.P., F.D.L., and S.D. Critical revision of the article for important intellectual content: All authors. Statistical analysis: G.P., F.D.L. Administrative, technical, or material support: F.B., B.B., E.B., and A.M. Supervision: S.D., E.B., F.D.L., and G.P.

## Acknowledgments

The authors thank all participants who donated their time to take part in this study.

### Author Disclosure Statement

No conflict of interest to be reported for any of the coauthors.

### Funding Information

This study was registered in the Iranian Registry of Clinical Trials (identifier IRCT 20210708051817N1). The authors have no conflicts of interest to disclose. This research received no funding.

### References

- Huynh PP, Ishii LE, Ishii M. What is anosmia? *JAMA* 2020;324:206.
- Meng X, Dai YZ, Meng Z. COVID-19 and anosmia: A review based on up-to-date knowledge. *Am J Otolaryngol* 2020;41:102581.
- Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): A multicenter European study. *Eur Arch Otorhinolaryngol* 2020;6:1–11.
- Paderno A, Schreiber A, Grammatica A, et al. Smell and taste alterations in COVID-19: a cross-sectional analysis of different cohorts. *Int Forum Allergy Rhinol* 2020;10:955–962.
- O'Byrne L, Webster KE, MacKeith S, et al. Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction. *Cochrane Database Syst Rev* 2021;7:CD013876.
- Gerkin RC, Ohla K, Veldhuizen MG, et al. Recent smell loss is the best predictor of COVID-19: A preregistered, cross-sectional study. *medRxiv [Preprint]* 2020;26:2020.07.22.20157263.
- Lechien JR, Chiesa-Estomba CM, Beckers E, et al. Prevalence and 6-month recovery of olfactory dysfunction: A multicentre study of 1363 COVID-19 patients. *J Intern Med* 2021;290:421–431.
- Carvalho-Schneider C, Laurent E, Lemaigen A, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect* 2021; 27:258–263.
- Lee DJ, Lockwood J, Das P, et al. Self-reported anosmia and dysgeusia as key symptoms of coronavirus disease 2019. *CJEM* 2020;22:595–602.
- Hua-Huy T, Lorut C, Aubourg F, et al. Persistent nasal inflammation five months after acute anosmia in patients with COVID-19. *Am J Respir Crit Care Med* 2021;203: 1319–1322.
- van Riel D, Verdijk R, Kuiken T. The olfactory nerve: A shortcut for influenza and other viral diseases into the central nervous system. *J Pathol* 2015;235:277–287.
- Aragao MFVV, Leal MC, Cartaxo Filho OQ, et al. Anosmia in COVID-19 associated with injury to the olfactory bulbs evident on MRI. *Am J Neuroradiol* 2020;41:1703–1706.
- Chetrit A, Lechien JR, Ammar A, et al. Magnetic resonance imaging of COVID-19 anosmic patients reveals abnormalities of the olfactory bulb: Preliminary prospective study. *J Infect* 2020;81:816–846.
- Zheng J, Wong LR, Li K, et al. COVID-19 treatments and pathogenesis including anosmia in K18-hACE2 mice. *Nature* 2021;589:603–607.
- Eliezer M, Hamel AL, Houdart E, et al. Loss of smell in patients with COVID-19: MRI data reveal a transient edema of the olfactory clefts. *Neurol* 2020;95:e3145–e3152.
- Le Bon S-D, Konopnicki D, Pisarski N, et al. Efficacy and safety of oral corticosteroids and olfactory training in the management of COVID-19-related loss of smell. *Eur Arch Otorhinolaryngol* 2021;278:3113–3117.
- Bouzigon R, Grappe F, Ravier G, Dugue B. Whole- and partial-body cryostimulation—cryotherapy. Current technologies and practical applications. *J Therm Biol* 2016;61: 67–81.
- Banfi G, Melegati G, Barassi A, et al. Effects of whole-body cryotherapy on serum mediators of inflammation and serum muscle enzymes in athletes. *J Therm Biol* 2009;34: 55–59.
- Borm G, Fransen J, Lemmens W. A simple sample size formula for analysis of covariance in randomized clinical trials. *J Clin Epidemiol* 2007;60:1234–1238.
- Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York, NY: Routledge Academic, 1988.
- Harless L, Liang J. Pharmacologic treatment for postviral olfactory dysfunction: A systematic review. *Int Forum Allergy Rhinol* 2016;6:760–767.
- Lubkowska A, Szygula Z, Chlubek D, Banfi G. The effect of prolonged whole-body cryostimulation treatment with different amounts of sessions on chosen pro- and anti-inflammatory cytokines levels in healthy men. *Scand J Clin Lab Invest* 2011;71:419–425.
- Tindle HA, Davis RB, Philipps RS, Eisenberg DM. Trends in use of complementary and alternative medicine by US adults: 1997–2002. *Altern Ther Health Med* 2005;11:42–49.

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