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Fatigue in post-acute sequelae of SARS-CoV2 (PASC) treated with oxygen-ozone autohemotherapy – preliminary results on 100 patients

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Abstract. – OBJECTIVE: Post-acute sequelae of SARS-CoV2 infection (PASC) are a novel terminology used to describe post-COVID persistent symptoms, mimicking somehow the previously described chronic fatigue syndrome (CFS). In this manuscript, we evaluated a therapeutical approach to address PASC-derived fatigue in a cohort of past-COVID-19 positive patients.

PATIENTS AND METHODS: A number of 100 patients, previously diagnosed as COVID-19 positive subjects and meeting our eligibility criteria, was diagnosed having PASC-related fatigue. They were recruited in the study and treated with oxygen-ozone autohemotherapy (O2-O3-AHT), according to the SIOOT protocol. Patients' response to O2-O3-AHT and changes in fatigue were measured with the 7-scoring Fatigue Severity Scale (FSS), according to previously published protocols.

RESULTS: Statistics assessed that the effects of O2-O3-AHT on fatigue reduced PASC symptoms by 67%, as a mean, in all the investigated cohort of patients ($H = 148.4786$ $p < 0.0001$) (Figure 1). Patients following O2-O3-AHT therapy, quite completely recovered for PASC-associated fatigue, a quote amounting to about two fifths (around 40%) of the whole cohort undergoing ozone treatment and despite most of patients were female subjects, the effect was not influenced by sex distribution ($H = 0.7353$, $p = 0.39117$).

CONCLUSIONS: Ozone therapy is able to recover normal functionality and to relief pain and discomfort in the form of PASC-associated fatigue in at least 67% of patients suffering from post-COVID sequelae, aside from sex and age distribution.

Key Words:
COVID-19, PASC, post-COVID syndrome, Ozone therapy, Fatigue.

Introduction

COVID-19 causes severe systemic disorders. SARS-CoV2 infection damages endothelia leading to a possible immuno-thrombosis[1] and moreover, patients infected with SARS-CoV2, even after healing from the sickness, may suffer for long lasting discomforts, pain and fatigue, collectively classified as "Post-Acute Sequelae of SARS-CoV2 infection" or PASC[2]. Lowe et al., in a longitudinal prospective cohort encompassing 234 adults (177 entered the study), described these sequelae and assessed that the most common and persistent symptom was fatigue[2]. Fatigue is a leading marker of PASC in patients still suffering from consequences due to the previous COVID-19. These patients should be targeted by innovative therapeutic approaches in order to relieve fatigue, but novel suggestions to address this great concern in COVID-19 pandemic are yet far to be fully introduced. It seems that PASC cannot account on reliable therapy so far, representing a huge concern for managing post-COVID sequelae[3]. Moreover, PASC diagnosis too, represents a crucial matter of debate.

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To date, a reliable and feasible tool to investigate fatigue in PASC patients is individual's interview[4]. In this perspective, we approached the evaluation of PASC-related fatigue by using a modified Neuberger's FSS scoring questionnaire[5]. This method was introduced to assess the ability of an oxygen-ozone mixture *via* major auto-hemotransfusion (O_2-O_3-AHT) to reduce fatigue symptomatology in PASC patients. This brief report describes the results gathered from a clinical multicenter case series study.

Patients and Methods

Outpatients were randomly recruited from two highly experienced clinics (Pordenone and Bergamo), in order to reach the proper sample size for optimal statistics. Sample size was calculated to achieve an error range of about 10%. Referring to a population proportion of 51%, forecast data resulted in a 13.86% error with 50 patients, whereas 9.80% (<10%) with 100 patients, considering a 95% confidence probability. Major eligibility criteria were previous swab positivity to SARS-CoV2 infection, moderate to severe COVID-19, wide age distribution spanning (25-90 years), no previous chronic inflammation diseases or fatigue syndromes aside from PASC. Fatigue was classified as related to PASC instead of CFS by anamnestic and symptomatology criteria by one of the authors (UT), with renowned expertise in the field, and following also further criteria published elsewhere in the literature[6].

Briefly speaking, a cohort of 100 Caucasian outpatients were examined at the Clinical Medial Group Pordenone and the Comunian Clinics, Bergamo (mean age 55.21 yrs ±12.72, IC_{95} = 52.72-57.70). Patients experienced COVID-19 in the previous 6 months and were currently suffering from post-COVID-19 fatigue. They were evaluated with a 7-scoring system Fatigue Severity Scale (FSS) before undergoing therapy[5] (Table IA). Patients signed an informed consent, prior to entering the study, following any ethical criteria from the Declaration of Helsinki. Upon the enrollment, recruited subjects were all SARS-CoV2 negative, did not take therapeutic drugs within the previous 72 hours, did not show either signs, or symptoms or diagnosis of tumors and other chronic immunological syndromes not related to the previous COVID-19. Following FSS questionnaire, patients underwent a pivotal therapy with at least one treatment of O_2-O_3 autohemotherapy (AHT) (2 patients), and usually 2-3 O_2-O_3AHT (major) treatments each week for 2–3 weeks (40-50 mg/150-200 ml ozone into 150/200 ml blood), according to previously published reports regarding SIOOT panels[7,8]. Following treatments, patients were interviewed with FSS at least one week later, to avoid placebo effects. Statistics were evaluated on mean ± standard deviation (SD) for quantitative values (ages) and a Kruskall-Wallis test (p<0.05) for scores was applied.

Results

Table IB summarizes the leading results obtained from this preliminary study. All treated patients, except three of them (with very modest changes), strongly ameliorated their health status. Patients with the highest FSS score before treatment accounted for 74%, of which 54/74 = 72.97% female subjects. The percentage of the highest FSS delta score, calculated as the difference between $FSS_{pre\text{-}treatment}$ and $FSS_{post\text{-}treatment}$, ($\Delta_{FSS}$ = - 6), was 36%, following O_2-O_3-AHT, whereas the lowest (Δ_{FSS} = - 1), amounted to 3%, with Δ_{FSS} = - 2, accounting for 9%. The 85% of patients reported a FSS amelioration from 7 to at least 3. Statistics assessed that O_2-O_3-AHT reduced PASC symptoms, i.e., fatigue, by at least 67% (as a mean), in all the investigated cohort of patients (H = 148.4786 p < 0.0001) (Figure 1). Patients following O_2-O_3-AHT therapy, quite completely recovered for PASC-associated fatigue, representing a quote amounting to about two fifths (around 40%) of the whole cohort undergoing ozone treatment and despite most of patients were female subjects, the effect was not influenced by sex distribution (H = 0.7353, p = 0.39117). This evidence prevents any criticism about the possibility of feeling different degrees of fatigue due to different sex-linked psychological attitudes towards subjective pain or discomfort. Furthermore, significant effects did not depend on age distribution, as either in very old patients (≥ 75 years old) or in youngest ones (≥ 50 years old), statistics reported similar distributions in FSS between patients before and after the O_2-O_3-AHT (Table I).

Discussion

Treatment with O_2-O_3-AHT improved fatigue symptoms in all the tested patients, though with different degrees. The highest effect was observed

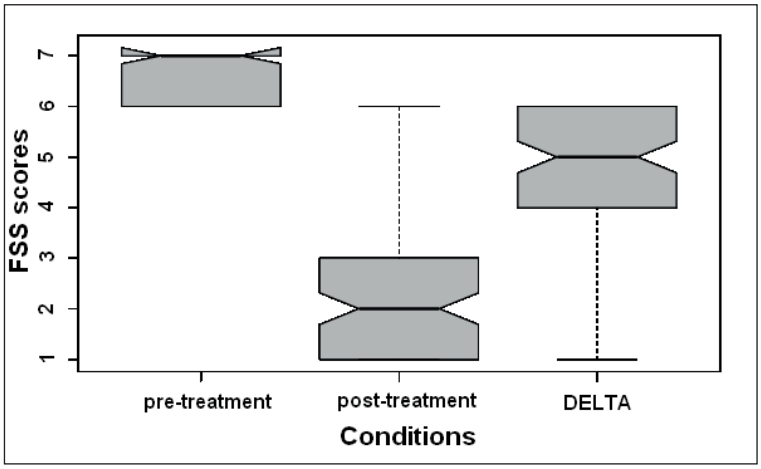

Figure 1. Notched box plots of FSS scoring in patents with post-COVID fatigue before and after oxygen ozone therapy. (H = 148.4786 ($p < 0.0001$) The delta Notched box plot shows how the difference in post-COVID symptoms is very high.

Table I. Results of PASC-associated fatigue in patients treated with O_2-O_3 AHT.

Table IA. FSS questionnaire.

Read and circle a number	***Strongly disagree → Strongly agree***
1 My motivation is lower when I am fatigued	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
2 Exercise brings on my fatigue	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
3 I am easily fatigued	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
4 Fatigue interferes with my physical functioning	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
5 Fatigue causes frequent problems for me	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
6 My fatigue prevents sustained physical functioning	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
7 Fatigue interferes with carrying out certain duties and responsibilities	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
8 Fatigue is among my most disabling symptoms	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7
9 Fatigue interferes with my work, family and social life	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Table IB. Data about patients undergoing O_2-O_3-AHT

Sex distribution	Age distribution	Kruskall-Wallis test (whole)
Males 30 Females 70	< 30 yrs 4 31<x<50 36 51<x<64 35 ≥65 25	H = (12/(N(N+1)) * ($\sum T^2/n$) - 3(N+1) H = 0 * 2517453.38 - 603 H = 148.4786 p< 0.0001 (Δ_{b-a}) Fatigue reduction in PAS = 67%
Kruskall-Wallis test		
Age ≥ 75 yrs (very old)	Age ≤ 50 yrs (very young)	Incidence of sex ratio (F)
H = (12/(N(N+1)) * ($\sum T^2/n$) - 3(N+1) H = 0.029 * 2675.45 - 63 H = 13.4414 The H statistic is 13.4414 (1, N = 20) p = 0.00025	H = [12/(N(N+1)] * ($\sum T^2/n$) - 3(N+1) H = 0.002 * 188769 - 255 H = 62.2588 The H statistic is 62.2588 (1, N = 84). p<0.00001	H = [12/(N(N+1)]* ($\sum T^2/n$) - 3(N+1) H = 0.003 * 56039.267 - 183 H = 0.7353 The H statistic is 0.7353 (1, N = 60).p = 0.39117

FSS questionnaire and the H statstics of the Kruskall-Wallis test; H = Kruskall-Wallis statistics. Under the null hypothesis the chi square distribution approximates the distribution of H.

in about 36% of PASC patients but at least 85% of them experienced an improvement from FSS = 7 to FSS = 3. Preliminary results described in this report showed that O_2-O_3-AHT reliefs fatigue associated with PASC. The recovery from PASC, assessed as an improved health status and well-being, with an evident reduction in fatigue and discomfort, lasted also several months following therapy. At the best of our knowledge no data about the effect of medical ozone in PASC-associated fatigue has ever been reported before. In this paper about two fifths of the patients' population recovered their healthy functionality and felt much better than before. Ozone therapy was successfully used to treat COVID-19 in our group[8], and its therapeutic suggestion was forwarded starting from this evidence. Nowadays, it is particularly hard for us to highlight and fully elucidate which mechanism underlies this encouraging and significant result, although some hypothesis can be forwarded by retrieving evidence from other chronic fatigue syndromes.

A very recent paper by Blauersteiner et al[9], associated the CFS-caused fatigue with endothelial dysfunction and vascular alterations, often related to disorders in the silent information regulator 1 and endothelial nitric oxide synthase (Sirt1/eNOS) axis. In particular, the microRNAs miR-21, miR-34a, miR-92a, miR-126, and miR-200c were found to be abundant in CFS patients' plasma respect to healthy controls[9]. Mir-21 is involved in the immune response[10] and mir-34a is involved in both endothelial and inflammatory signals, even in COVID-19, as its modified form mir-34a-5p was found as associated with endothelial dysfunction (observed in postmortem cases) in SARS-CoV2 infected individuals[11]. If fatigue may depend on endothelial dysfunction, as observed in CFS[12], ozone can exert a fundamental action on endothelia[13]. While the most recent evidence[14] assesses that COVID-19 has an endothelial and immuno-thrombotic etiopathogenesis, the role of oxygen-ozone in the regulation of the endothelial-thrombotic mechanisms may be particularly intriguing, deserving further attention by clinical research, particularly for its action on the nitric oxide (NO) pathway[13]. Interestingly, O_2-O_3-AHT works perfectly not only in CFS[15] but also in fibromyalgia, where the role of NO seems to be particularly relevant[16,17].

Fundamentally, ozone was successfully used for chronic fatigue syndrome[15], a pathological disorder with several hallmarks shared with PASC and involving many organs functions[18-20], and it is conceivable that ozone therapy can offer promising expectations even to PASC-associated fatigue.

However, further research is requested. This preliminary study has some limitations. A deeper insight on the pre-clinical data in order to assess the evidence reported may be particularly useful. Confounders, due to clinical status, should be statistically calculated and reported. The possibility to increase the cohort of subjects undergoing the study is the next planning perspective.

Conclusions

Ozone therapy is able to recover normal functionality and to relief pain and discomfort in the form of PASC-associated fatigue in at least 67% of patients suffering from post-COVID sequelae, aside from sex and age distribution. This preliminary evidence encourages further research to go ahead in deepening the mechanisms underlying these results.

Conflicts of Interest

The authors state they have no conflicts of interest.

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