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Whole-body cryotherapy – promising add-on treatment of depressive disorders

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Summary

Aim. New, effective biological interventions for treatment of depressive episodes and recurrent depression are still needed. Whole-body cryotherapy (WBC), which is a treatment using cryogenic temperature, is a novel therapeutic modality in neurology and rheumatology. The objective of this study was to determine the efficacy and safety of WBC as an add-on treatment for depressive episode.

Method. 30 adults diagnosed with depressive episode were recruited to an observational, prospective study. 21 participants (17 women, 81%), mean age 46.1 (±16.7), completed the whole study procedure. The Hamilton Depression Rating Scale and the Beck Depression Inventory were used to assess the severity of depressive symptoms. Additionally, quality of life and anhedonia were assessed with the WHOQoL-BREF and the SHAPS. Participants undertook 10, 2-minute (from – 110 C to – 135 degrees C) WBC sessions within two weeks.

Results. Patients after WBC sessions showed significant improvement in the form of a reduction in total scores in scales assessing depressive symptoms: the HDRS ($p< 0.00001$) between T1 (16.94±4.3) and T4 (4.50±4.2) and the BDI-II (T1: 13.48±4.6; T4: 6.14±6.7, $p< 0.03$), lower anhedonia level on SHAPS ($p = 0.011$) and higher quality of life in the following domains: physical health ($p = 0.024$), psychological health ($p = 0.016$) and environmental domain ($p = 0.003$). Pre/post comparison of self-report well-being measured by the VAS scale showed a significant increase ($p< 0.00001$). It was shown that WBC have no effect on the level of cytokines, NO, hsCRP, ESR and TAS in blood ($p> 0.05$).

Conclusions. WBC proved to be an effective, safe, and tolerable add-on intervention in patients with depressive episode. Further randomized controlled trials should be conducted.

Key words: whole-body cryotherapy, depression

Introduction

According to the World Health Organization, over 300 million people around the world are affected by depression, which was the third leading cause of disability in 2015. Moreover, it has been revealed that prevalence of depression increased by 18.4% between 2005 and 2015 [1, 2]. Overall mortality is two-time higher in people who suffer from depression. Depression influences decreased life expectancy, especially by presence of comorbid substance abuse or somatic illness [3]. Available pharmacological and psychological treatments for depression are only moderately effective in 70% of patients [4].

Recently published reviews and meta-analyses suggest that anti-inflammatory treatments could have a significant role in the treatment of depressive symptoms [5–8]. Additionally, meta-analysis of Więdłocha et al. [9] showed that plasma levels of IL-4, IL-6 and IL-10 decreased in patients with major depressive disorder after antidepressant treatment. Depression is also associated with high CRP level [10] and decreased NO level [11, 12] as well as higher activity level of antioxidant enzymes [13]. Hence, further studies on the possible adjuvant treatment with anti-inflammatory activity in depression treatment are needed.

Whole-body cryotherapy (WBC) involves repeatable, transient, 1–4-minute exposure to extremely cold air (temp. between – 110 to – 160°C) in special cryochambers. Several lines of evidence indicate that WBC can be profitable for patients suffering from rheumatoid arthritis, fibromyalgia, ankylosing spondylitis, multiple sclerosis, chronic low back pain as well as depression and anxiety disorder [14]. Therefore, the possible effect of WBC on inflammation mechanism has been considered. Current literature suggests that WBC has mobilization effects on immunological system. WBC increases level of anti-inflammatory cytokines IL-6 and IL-10, as well as decreases level of IL-1α [15]. Moreover, it has been revealed that after WBC sessions the total antioxidative status (TAS) level was decreased. Sutkowy et al. [16] also observed decrease in oxidative stress markers after WBC exposition combined with exercise.

Heretofore, there is limited data about associations between whole-body cryotherapy and mental health. Little is known about the improvement of sleep efficiency and duration after WBC [17, 18]. Similarly, the influence of WBC on mood disorders has not been the purpose of many research [19, 20] and the mechanisms of action are still unknown.

Thus, the aim of this study was to determine whether extreme low temperatures may beneficially influence mood, quality of life as well as biochemical factors of the people who are diagnosed with depressive episode.

Methods

The research protocol for this experimental pilot study was reviewed and received approval from the Bioethical Committee (permissions numbers: KB-406/2014 and KB-252/2015). The project was conducted within the framework of research aimed at promoting young scientists, funded by the Ministry of Science and Higher Education (registration number Pbmn 167) in cooperation with Creator Sp. z o.o.

Participants

Eligible patients for the study had to be at least 18 years old with diagnosed depressive episode (F.32, F.33 according to research criteria of the International Classification of Diseases, ICD-10).

The exclusion criteria were as follows: psychosis, alcohol and drug abuse, dementia, inability to understand questions and written information, standard contraindications to use WBC (e.g., claustrophobia, cryoglobulinemia, Raynaud's disease, hypothyroidism, acute respiratory diseases, cancer, acute cardiovascular disease like coronary disease, circulatory insufficiency, deep vein diseases, purulent skin changes, neuropathies, cold intolerance) and previous exposition to WBC.

All participants received oral and written information about the study design, anonymity and gave the written consent.

The psychiatric examination was performed by an experienced certified psychiatrist. The participants were receiving a stable pharmacological regimen (SSRI or SNRI in therapeutic doses) within outpatient psychiatric care, without changes during the study.

There were 30 participants recruited – out of which 21 persons completed the whole study. Seven people resigned from the study before starting WBC sessions (declaring lack of time, claustrophobia). One patient was absent for WBC more than three times and 1 patient had to stop treatment because of hypertension.

We prospectively evaluated depressive symptoms and quality of life of 21 people (17 women, 81%, mean age 46.1±16.7) with depressive episode (F.32, F.33; ICD-10) in outpatient clinics. There were no episodes of treatment-emergent adverse events during the study, which was carefully monitored. There were no somatic or mental adverse events, except for localized skin redness of one patient who continued the WBC after medical consultation.

Procedure

A cryotherapy chamber (CR 2002, Wroclaw type, provided by Creator Sp. z o. o.), cooled by liquid nitrogen consists of two rooms: the vestibule/antechamber (temperature – 60ºC) and the proper chamber (temperature – 110ºC on the first days

to – 135ºC further on). There is no direct contact with the liquid nitrogen in this type of device.

The usual WBC session lasts for 2 minutes in the main chamber with 30 seconds extra for adaptation in the vestibule before and after the proper session. Each procedure is under control by the personnel.

A group of 5–6 people usually uses the device at the same time. Participants are required to wear shorts and t-shirt, gloves, headband or beanie, a nose and mouth mask, high-knee socks and wooden shoes. This outfit should be woollen or cotton to reduce the risk of injuries caused by cold. Before every WBC session participants had the blood pressure measured.

Participants undertook 10 whole-body cryotherapy sessions for two weeks (Monday–Friday). There were 4 assessment points during the study – before the first WBC session (T1), after 6th session (T2), after the last WBC (T3) and two weeks later (T4) as follow-up. Psychiatric evaluations were conducted at T1 and T4. Blood examination was done at T1 and T3. The detailed structure of the procedure is presented on the Figure 1.

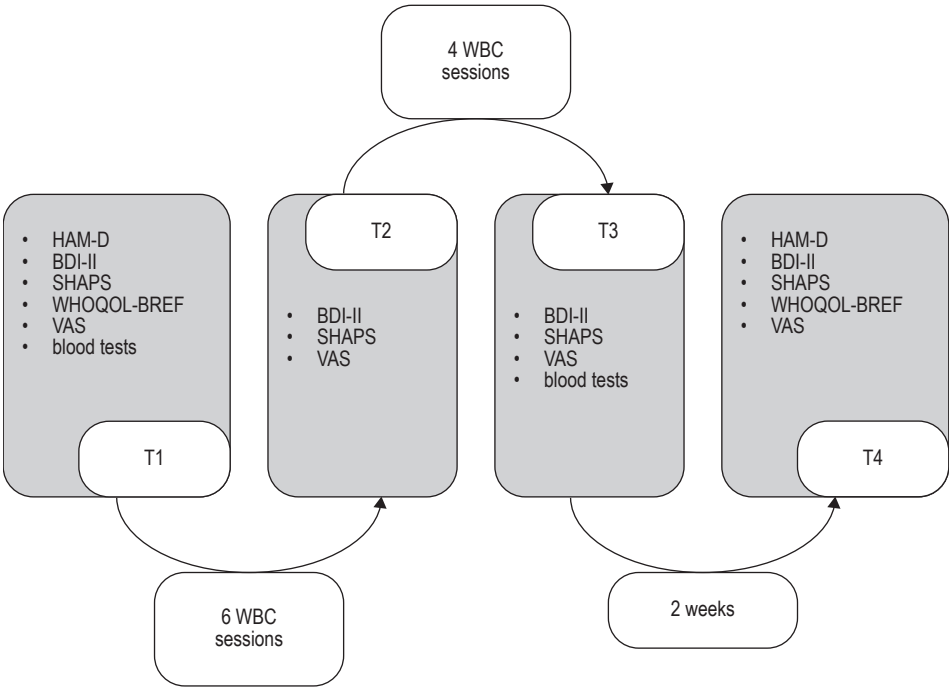


Figure 1. **The study design**

Instruments

The Hamilton Depression Rating Scale (HDRS) is a widely used tool to measure depressive symptoms in psychiatry. There are two versions available – 17 and 21 items. Regarding the fact that the last 4 items are not assessing the depressive symptoms, the shorter version was used in this study. All symptoms are scored between 0 and 4. The total score under 7 points suggests lack of disorders. The score of 7–12 points is considered to be mild depressive disorder, 13–17 – moderate, 18–29 – severe, and 30–52 very severe [21].

The Beck Depression Inventory (BDI-II) [22] is used in psychiatry for the diagnosis of depressive symptoms. It has a good tool for assessing depressive symptoms as well as the severity of depressive disorder. The BDI-II consists of 21 items scored between 0 (lack of symptoms) and 3 points (the highest severity of the described symptom). Total score between 0 and 11 indicates the lack of depressive symptoms, 12–26 – mild depressive episode, 27–49 – moderate depressive episode and 50–63 – severe depressive episode [23].

The World Health Organization Quality of Life – BREF (WHOQOL-BREF) [24] was created based on the WHOQOL-100 by the World Health Organization as the universal tool to assess the quality of life. It is commonly used among healthy people as well as patients diagnosed with different diseases, both for clinical and scientific purposes. It consists of 26 items. Two questions are about individual, general quality of life and health. 24 items are gathered into 4 domains: physical, psychological, social and environmental one. All items are scored between 1 and 5. Higher total score indicates better life quality. The WHOQOL-BREF was adapted into Polish by Wołowicka and Jaracz [25].

The Snaith-Hamilton Pleasure Scale (SHAPS) for the assessment of anhedonia, one of key symptoms of depression [26], is a short, 14-item self-administered questionnaire. It consists of 4 domains: interests, social interactions, sensual experiences, and food/drinks. All items are scored between 0 and 1. The score of 3 or higher seems to indicate the lower level of pleasure experience (anhedonia) which can help to differentiate people with depressive disorders from healthy population.

The Visual Analogue Scale (VAS): Self-report on well-being including: mood, level of motivation and sleep quality, were included in the mental health assessment. For the results the mean score from all three parts was considered. Participants were asked to cross a vertical line between two extreme points (0 – the worst mood and 10 – the best mood).

Biochemical measurements

Whole blood samples (15 ml) were collected from the participants at T1 and T3 in order to evaluate the level of cytokines, nitric oxide (n = 20) in plasma, hsCRP, TAS

($n = 21$) in serum and ESR. The levels of cytokines (IL-6, IL-10) and nitric oxide (NO) were determined by ELISA and by Griess reaction, respectively. ESR (erythrocyte sedimentation rate) was measured by S-Sedivette® Enclosed ESR System (Sarstedt, Germany), TAS – by TAS Randox kit (United Kingdom) and hsCRP – by CRP High Sensitivity kit (DiaSys, Germany) were measured using Konelab 20i (ThermoScientific, USA) autoanalyzer.

Statistical analysis

The statistical analysis was performed using R software for Windows version 3.3.1. [27] and Statistica 13.PL (StatSoft, Poland). The Shapiro-Wilk test and visual assessment were used to analyze the normality of distribution. Changes in time in quantitative variables were assessed using the Wilcoxon test for paired data (for two time points), or using the Friedman test with *post-hoc* analysis using Conover method (for multiple time points). Changes in time in qualitative variables were assessed using the Cochran's Q test with the use of repeated measurements of the Wilcoxon sign-rank test. Differences were considered as statistically significant at the p-value less than 0.05.

Results

Study sample characteristics

Out the recruited sample of 30 people, 21 participants completed the whole study procedure. Women accounted for 80% of the study sample ($n = 17$). The mean age was 46.1 (±16.7). The majority of population completed higher education ($n = 11$; 52.4%), lived in the small town or big city ($n = 20$; 95.2%). The mean time of being diagnosed with depressive disorder was 5.3 (±7.5) years. Severity of depressive symptoms at baseline was 16.94 (±4.29) in the HDRS and 23.57 (±7.31) in the BDI-II.

Depressive symptoms

Comparison of depressive symptoms measured by HDRS at different time points showed a statistically significant difference (Wilcoxon test, $p < 0.00001$) (Figure 2).

Taking into account the mean BDI-II score in 4 measure-points, a significant decrease in the total score can be observed along with each assessment (T1: 25.57±7.3; T2: 14.67±8.6; T3: 10.90±9.1; Friedman test with Conover *post-hoc* method, $p < 0.00001$) and maintenance of this change after 2 weeks since the last WBC (T4: 10.52±10.2). A similar observation is visible for the cognitive domain of the BDI-II (T1: 13.48±4.6; T2: 8.19±5.7; T3: 6.71±5.8, Friedman test with Conover *post-hoc* method, $p < 0.0000$) with the fact that a significant change was found even 2 weeks after the last session (T4: 6.14±6.7, $p < 0.03$). With the use of the Friedman test with Conover *post-hoc* method a significant difference was observed for the somatic domain of the BDI-II

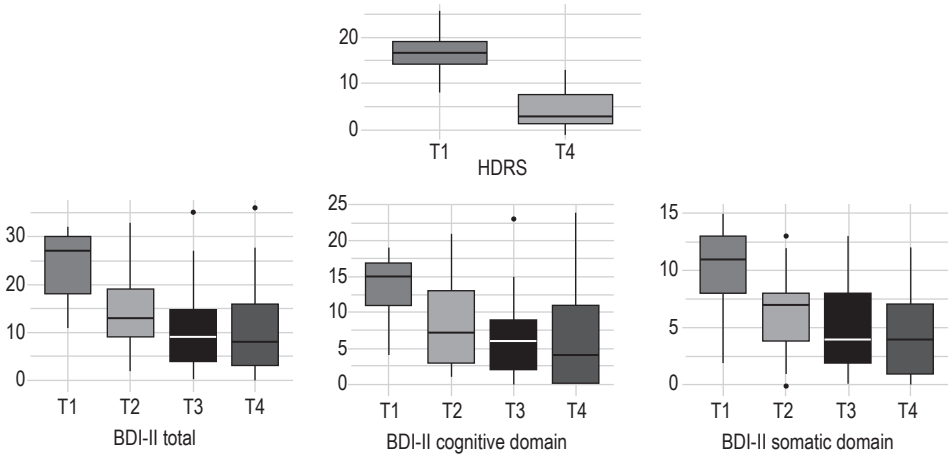


Figure 2. **The level of depressive symptoms as measured by the HDRS and BDI-II in 4 measure-points in the study sample**

between T1 (10.10±4.0) and T2 (6.48±3.4, $p < 0.04$), T3 (5.05±4.1, $p < 0.0006$), T4 (4.38±4.1, $p < 0.00001$).

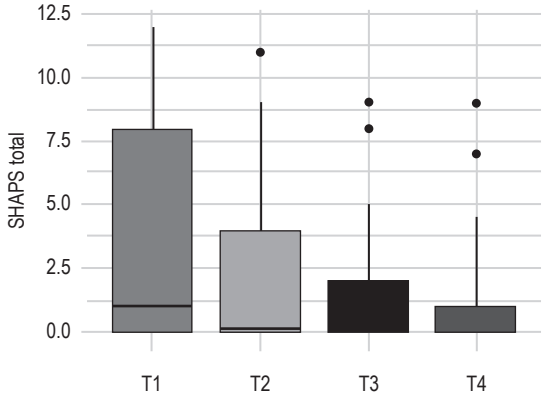
Anhedonia

Anhedonia is one of key criteria in diagnosis of depression. The statistical analysis showed that after WBC participants scored significantly lower on the SHAPS, which indicated their better ability to experience pleasure (Friedman test, $p = 0.011$, Figure 3). *Post-hoc* analysis with Conover method showed a significant difference between 3 measure-points (T1: 3.33±4.2; T2: 2.43±3.7; T3: 1.43±2.7) and the maintenance of this change after 2 weeks since the last WBC (T4: 1.19±2.5, $p = 0.2$).

The obtained results showed that after WBC along with the next measure-points, significantly fewer participants experienced anhedonia (Cochran's Q test, $p = 0.029$, Figure 4). Symptoms of anhedonia were found in 43% ($n = 9$) of the study group at T1, and after cryostimulation at points T3 and T4 they were found only in 19% ($n = 4$) of the study group.

General well-being and quality of life

Comparison of self-reported well-being (including: mood, level of motivation and sleep quality) at different time points showed a statistically significant increase in the total mean VAS scores (T1: 3.24±1.6; T2: 4.64±1.7; T3: 6.09±1.7; Friedman test, $p < 0.00001$, Figure 5) after WBC.



	T1	T2	T3
T2	0.0329		
T3	0.0000	0.0027	
T4	0.0000	0.0001	0.2220

Figure 3. **The level of anhedonia as measured by the SHAPS in 4 measure-points in the study sample**

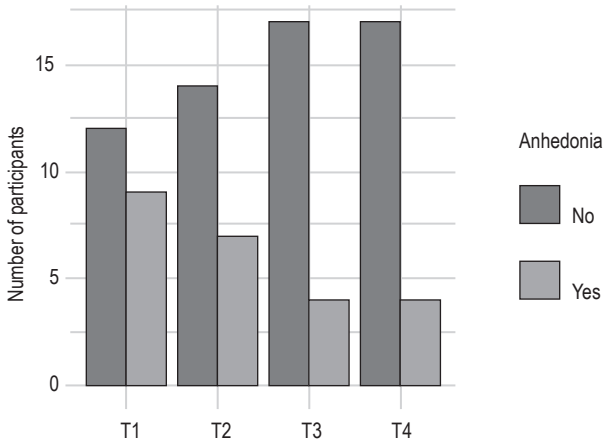


Figure 4. **The distribution of the number of participants who experienced symptoms of anhedonia identified by the SHAPS in 4 measure-points**

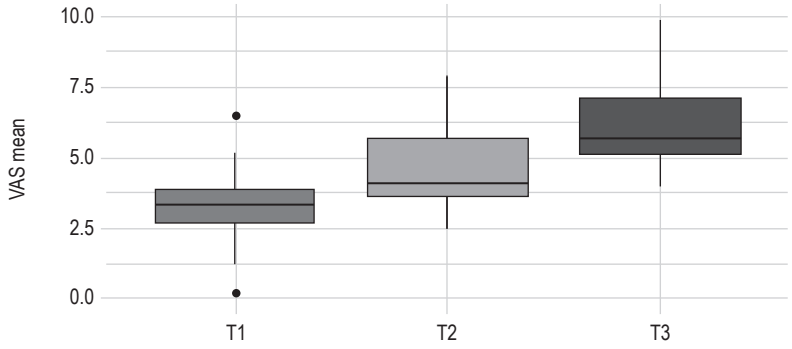


Figure 5. **The level of self-reported well-being as measured by the VAS in 3 measure-points in the study sample**

Comparison of the quality of life in the study sample at different time points is presented in Table 1. Significant differences are observed between T1 and T4 in: physical health (p = 0.024), psychological health (p = 0.016) and environmental (p = 0.003) domains.

Table 1. **Quality of life before and after WBC in the study sample**

WHOQoL-BREF	T1	T4	p-value Wilcoxon test
	Mean ± SD		
Physical health	40.75 ± 14.5	51.20 ± 13.2	0.024
Psychological health	48.30 ± 10.3	57.60 ± 15.1	0.016
Social relations	47.50 ± 19.1	58.45 ± 27.2	0.060
Environmental	55.70 ± 15.8	67.90 ± 20.1	0.003

Abbreviations: WHOQoL-BRE – the World Health Organization Quality of Life-bref;
T1 – before whole-body cryostimulation; T4 – 2 weeks after last whole-body cryostimulation

The assessment of biological markers of inflammatory and antioxidant status

The values of biochemical parameters assessed in blood before (T1) and after (T3) exposure to WBC are presented in Table. 2. Analysis by Friedman test showed that WBC had no effect on IL-6, IL-10, NO, ESR and hsCRP concentration ($p > 0.05$). Moreover, there were no significant differences in total antioxidative status (TAS, $p > 0.05$).

Table 2. **Biochemical parameters: ESR, hsCRP, TAS, IL-6, IL-10, and NO in blood before and after WBC**

Parameter	**T_1 median (Q1–Q3) mean ± SD**	**T_3 median (Q1–Q3) mean ± SD**	p
ESR [mm/h]	10.0 (5.0–14.0) 11.5 ± 6.3	11.0 (7.0–16.0) 11.9 ± 6.3	0.371
hsCRP [mg/L]	1.04 (0.61–2.83) 2.04 ± 2.23	0.96 (0.56–1.90) 2.20 ± 3.12	0.275
TAS [mmol/L]	1.48 (1.44–1.55) 1.50 ± 0.10	1.52 (1.44–1.55) 1.50 ± 0.08	0.818
IL–6 [pg/ml]	0.00 (0.00–9.24) 28.17 ± 96.52	0.00 (0.00–10.30) 31.25 ± 114.60	0.944

table continued on the next page

IL–10 [pg/ml]	5.60 (4.11–7.26) 6.63 ± 5.38	5.64 (4.80–7.49) 7.04 ± 4.71	0.936
NO [nM]	492.06 (269.47–1025.47) 682.71 ± 600.64	700.61 (355.70–1165.85) 771.40 ± 545.33	0.809

Discussion

Considering the growing interest in whole-body cryotherapy in medicine, particularly in neurorehabilitation, neurology and rheumatology, the purpose of this study was to preliminary investigate the influence of whole-body cryotherapy on the course of treatment of depressive episode and its potential beneficial anti-inflammatory and antioxidative capacity.

The obtained results showed that the level of depressive symptoms significantly decreased after WBC in the self-assessment VAS scale as well as in psychiatric evaluation. Moreover, 10 sessions of WBC caused not only reduction in depressive symptoms but also simultaneous increase in general well-being, quality of life and ability to experience pleasure (reduction in anhedonia). This evidence confirmed the beneficial impact of WBC on depressive disorders [19, 20], fatigue and functional status [28] as well as mental state and quality of life [29] of people undergoing cryostimulation.

In the midst of heterogeneous nature of depression, in the recent reviews of studies [5, 30] regarding the relationship between mood disorders and immune-related abnormalities, it has been found that in some patients with depression there is a correlation between depressive symptoms and high levels of pro-inflammatory cytokines, such as IL-1, IL-1β, IL-6, tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and hypothalamic-pituitary-adrenal axis (HPA) hyperfunction. Pro-inflammatory cytokines are an important factor affecting the functioning of serotonergic system and the hypothalamic-pituitary-adrenal axis.

Moreover, Kitagami et al. [31] showed that cytokines may influence dopamine. In fact, intramuscular injection of IFN-α induced NO synthesis, which suppressed the level of tetrahydrobiopterin biosynthesis and dopamine production in rats. Additionally, the results obtained by Pasco et al. [32] supported the role of inflammatory processes in the course of depression and indicated elevated hsCRP level in the serum as a risk marker of major depressive disorder. There is considerable evidence indicating that cryostimulation can have an impact on pro – and anti-inflammatory cytokines levels [15, 33, 34]. Some researchers reported increased level of Il-6 and Il-10 back to baseline amount after 2 weeks [33] or lack of effect in Il-6 and increase in Il-10 level [34, 35]. In a study of Dulian et al. [36], a decrease in hsCRP level was reported, however, hsCRP levels were unchanged in results obtained by Banfi et al. [37].

Furthermore, mood disorders are associated with oxidative and nitrosative stress [36]. Formation of reactive nitrogen species (RNS) causes disturbances of antioxidative mechanisms balance, damage of fatty acids, proteins, DNA, and finally the cell by RNS [38]. Stanek et al. [39] observed significant decrease of oxidative stress and increase of antioxidative parameters (e.g., TAS). Other findings reveled that cryostimulation may decrease oxidative stress [15, 40]. Miller et al. [40] observed that the level of total antioxidative status of plasma was decreased in depressive patient suffering from multiple sclerosis comparing to those without depression.

In this study the preliminary hypothesis that exposition to extreme low temperatures can affect the level of cytokines, NO, hsCRP was not confirmed. Il-6 is a main stimuli of acute phase proteins production, mainly CRP in the liver. The lack of changes in IL-6 concentration observed in our study probably determines a lack of changes in CRP concentration, and the stable level of IL-10, an anti-inflammatory factor, also confirms the lack of significant change in the severity of the inflammatory reaction in the body during WBC. Our results showed that inflammatory response during WBC is stable in depressive patients enrolled in this study and the same trend was revealed for antioxidative marker. Those observations suggest the need to compare the results with a control group, which is missing in this study, but is planned for the next stage of the project.

The present study has certain limitations. Firstly, this was a real-world experiment carried out as observational small-sample pilot study. We are fully aware that, in order to assess whether the intervention is effective, the variables should be compared with a control group. Additionally, it is important to note that this was an "add-on" study. The patients were treated with antidepressants for at least 4 weeks before WBC, which was assessed as a method complementary to or potentiating pharmacological treatment. Patients qualified for this procedure were at stable psychopharmacological treatment in outpatient clinic without any changes in dosages during the study. People with severe or drug-resistant depression were not qualified for this study. Due to the lack of a control group, it is difficult to assess whether the clinical improvement was an effect of longer time of medication use and not the use of WBC alone.

Also, other factors could cause the improvement among participants and they need to be mentioned because of the lack of the control group. For example, placebo effect could be related to the invitation into experimental treatment perceived by participants as an additional activity in their daily routine for two weeks. The patients also obtained extra time and interest from the doctor. Moreover, whole-body cryotherapy sessions were linked to new social contacts with other participants.

Moreover, the experimental group seemed to be rather homogeneous, however, the majority of patients were women. This limitation can influence the level of cytokines considering the general population and different types of depression. Additionally, it should be noted that our results concerned only blood measurements, which is

another limitation in regards to CSF samples and existence of the brain-blood barrier. Cytokines are capable of crossing the blood-brain barrier, however, it does not mean they can be functionally active [41]. An important element that may explain the incoherence of clinical improvement with cytokine results would be the fact that participants were using medications which could affect the regulation of inflammatory processes [42]. Therefore, the results obtained from blood call for caution when discussing findings, especially without possibility to refer to the control group results. Summing up, after obtaining positive results of the pilot study visible in the cognitive-behavioral sphere of the subjects, we can conclude that there is a need to conduct a pivotal study on WBC in mood disorders in a larger group of subjects, controlling for all the independent variables

Conclusions

This pilot study showed the significant reduction of pathological symptoms as well as improvement in quality of live among people with depressive episode exposed to cyclic intervention using extremely low temperatures. This study suggests that whole-body cryotherapy, may become a safe, effective and well-tolerated add-on treatment for people with depressive episode.

WBC may be considered as an additional treatment in depressive disorders among people without contraindications for exposure to extremely low temperatures. Further research is needed to confirm the effectiveness of WBC in a randomized controlled trial, and to identify potential mechanisms of action of extremely low temperatures.

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