

Whole-Body Cryostimulation in Fibromyalgia

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Currently, all available therapies for the control and management of fibromyalgia (FM) are mostly focused on relieving patients' symptoms and improving their quality of life. Thermal stress caused by cryostimulation induces an analgesic effect, improving pain, redox balance, and inflammatory symptoms in an exercise-mimicking fashion. In addition, it reduces the feeling of fatigue, improves mood, and reduces mental health deterioration with positive consequences on depressive states and improved sleep quality.

Keywords: whole-body cryostimulation ; fibromyalgia ; cryotherapy ; inflammation ; pain

1. Introduction

Fibromyalgia (FM) is a medical condition characterized by the combination of complex, sometimes indistinct, symptoms. FM manifestations include chronic widespread musculoskeletal pain and associated fatigue, morning stiffness, sleep disturbances ^{[1][2]}, depression, anxiety, and cognitive symptoms ^{[3][4]}, in line with the biopsychosocial model of pain ^[5], and evidence related to other chronic pain conditions ^{[6][7][8]}. In addition, FM is associated with psychological factors, such as neuroticism ^[9], alexithymia ^[10], catastrophizing ^[11], and low health-related quality of life ^[4], limiting people's daily activities as well as their social, professional, and recreational activities ^{[12][13]}. FM is the third most common musculoskeletal condition and is estimated to affect 0.2 to 6.6% of the adult general western population ^{[14][15]}. Due to its persistent and debilitating condition, FM imposes enormous economic burdens on society, as patients with FM have relatively high levels of comorbidities and high levels of health care utilization and cost ^[16].

Despite predisposing factors (genetic, stressful or traumatic events, viral infections, and obesity), the etiopathogenesis of FM is still not fully unraveled, making its diagnostic and classification criteria confusing. One of the most widely held hypotheses regarding the pathogenesis of FM is central sensitization to pain and deficits in endogenous pain-inhibiting mechanisms. Several studies in patients with FM have shown a lower threshold and tolerance for pain ^{[17][18]}, hyperalgesia and allodynia ^[19], a slower cognitive processing speed ^[20], a cortical or subcortical increase in pain processing compared with healthy subjects ^[21], and evidence of the presence of polyneuropathy in both small and large fibers ^[22]. All these symptoms suggest a neurogenic common origin characterized by an imbalance in the levels of neurotransmitters and consequently of the peripheral pro- and anti-inflammatory mediators ^[23]. Due to lack of agreement regarding its diagnosis, classification and etiopathogenesis, no consistently effective treatments are yet available. In many cases, FM has been seen as a "disease of misconnection" at different levels characterized by lack of specific biomarkers ^{[2][24]}.

In most cases, the therapeutic approach is characterized by multidisciplinary interventions that include patient's education, physiotherapy (including physical agents and exercise), pharmacological treatment, and psychotherapy ^[2]. Therapies for the management of FM are mainly focused on easing patients' symptoms and improving quality of life ^[25]. Although some studies have been conducted examining pharmacological and non-pharmacological interventions, treating patients with FM using a multimodal approach appears to be the most effective option even if more trials are needed ^[26]. Conventional pharmacological therapies usually rely on cyclic or chronic use of antidepressants, muscle relaxants, anti-inflammatories, and antioxidants ^[27]. Non-pharmacological measures consist of: (i) physiotherapy, including a variety of physical agents and land- or water-based physical exercise, such as aquatic or aerobic-based exercise, strength training (anaerobic exercise), and flexibility training; and (ii) psychotherapy, including cognitive-behavioral interventions, biofeedback, and psychological support ^{[28][29]}. With the growing recognition that there are different categories of FM with different clinical features, personalized prescription should be an important target to be achieved among the empirical and constantly evolving approaches that are proposed.

Whole-body cryostimulation (WBC) is a highly effective physical treatment mainly used in sports medicine to relieve pain, inflammatory symptoms, fatigue, and overuse symptoms due to its widely recognized anti-inflammatory and anti-oxidant effects ^[30]. Presently, it has been used as an add-on therapy in rheumatic (arthritis ^[30], fibromyalgia ^{[31][32][33][34][35][36][37]}

[38][39][40], and ankylosing spondylitis [41]), neurological (multiple sclerosis [42]) psychiatric (depression) [43], metabolic (obesity) [44], and diabetes [45]. WBC consists of exposure of a part or the whole body to very cold and dry air for generally 2 to 3-min. At present, there are two types of cryostimulation. Partial-body cryostimulation (PBC), where the body, excluding the head, is exposed to a cryogenic fluid injected and vaporized around the body inside a cryosauna, and the whole-body cryostimulation (WBC), performed inside a cryochamber, where the whole body is exposed to cold produced by cryogenic fluids or refrigerants [46]. Given the limited amount of published literature, here adopted studies performed with both a cryochamber and a cryosauna, all reported as "Whole-body Cryostimulation", despite knowing the different physiological reactions after PBC and WBC due to their large differences in internal temperatures measured with PBC having a higher gradient. The thermal stress elicited by cryostimulation generates vasoconstriction and stimulate the thermal receptors of the dermis by lowering skin temperature, and slowing down nerve conduction in pain fibers, which may be a way that cryotherapy induces an analgesic effect, relieving pain and inflammatory symptoms [47][48]. Moreover, it causes changes in the endocrine, circulatory, neuromuscular, and immunological system [49]. It provides homeostatic autonomic responses of thermogenesis and vasoconstriction by stimulating cold receptors and the thermoregulatory center in the hypothalamus from which efferent signals cause activation of the sympathetic system resulting in vasoconstriction followed by release of noradrenaline. Along with endorphins, norepinephrine modulates pain and slow conduction velocity of sensory nerve fibers such as C fibers, disabling the sensory receptors as well as their connections to proprioceptors [50]. An increase in parasympathetic cardiac control also occurs. Indeed, after cryostimulation, as a compensatory mechanism, downregulation of blood pressure [50], even overnight [51], may result in reduced feelings of fatigue, improved mood, and reduced mental health deterioration with possible positive consequences on depressive states, and improved sleep quality [43]. Recent literature has shown that WBC is immunostimulating and yields an anti-inflammatory response, with a decrease of the pro-inflammatory cytokines and increases of anti-inflammatory mediators [52][53][54][55][56][57]. It also appears to improve the effect on redox balance in a session/treatment number-, age-, and fitness-dependent manner [58], probably through the decrease in the total oxidant production which, consequently, induces antioxidant activity [56][58][59][60][61][62][63]. Thus, due to its widely recognized anti-inflammatory, antioxidant, analgesic, and exercise-mimicking effects [64], WBC is proposed as a promising add-on option in the multidisciplinary treatment of FM, considering also that diffuse inflammation is one of the sub mechanisms of depression [65], and that co-morbid depression is very common among FM patients, with a lifetime prevalence of 62–86% [66].

2. Clinical Effects of WBC in FM

Pain perception involves interconnected physiological and psychological mechanisms that include anatomical, physiological, cognitive, and affective components of pain [67]. There are two neural pathways that regulate pain signals: ascending pathways that transmit sensory signals through peripheral nerves, including nociceptive signals, to the spine and brain for processing; and descending pathways that send modulatory (excitatory and/or inhibitory) signals from the brain to the periphery, regulating ascending nociceptive signals that reach the brain [68]. These physical and noxious chemical signals are detected by nociceptors, specialized receptors in peripheral nerves activated by physical stimuli (i.e., changes in temperature, pressure, and impact). Many neurotransmitters and neurochemicals are involved in the transmission of pain signals such as norepinephrine and serotonin [69].

In FM, these two neural pathways operate abnormally causing an increased activity in the pain matrix which results in central amplification of pain signals, a phenomenon named central sensitization [70]. Several studies of FM-related pain and hyperalgesia have demonstrated the involvement of spinal mechanisms and an enhanced response to somatic and cutaneous stimuli throughout the brain's pain matrix, allodynia and hyperalgesia. In most cases, patients become hypersensitive to pain. The constant hypervigilance to pain can also be associated with psychological problems [71].

Most of the studies included in this review (7 out of 10) hypothesized that WBC should alleviate pain and/or inflammatory processes in FM patients, with the aim of improving health-related quality of life. These studies tested the therapeutic efficacy of WBC and its practicability for clinical routine in FM, also comparing it to other therapies (warm therapy or steam therapy) or treatments (antioxidants and analgesic agents).

All studies reported an analgesic effect of WBC with significant reduction in pain level, but had different settings. Bettoni et al. carried out two studies on the efficacy and safety of WBC in FM patients. The first report showed the superiority of WBC compared to antioxidants and analgesic agents, in terms of pain and fatigue reduction [34]. In the second study, patients performed aerobic exercise (cycle ergometer or treadmill) for 30 min immediately after WBC [33]. Physical activity, which is also used to treat FM, may have masked these results by opposing its induced vasodilation to WBC-induced vasoconstriction. In the cross-over trial of Rivera et al., the individuals' VAS and FIQ scores did not return to baseline after the first treatment with WBC due to too short wash-out periods, so that only results of the first sequence could be reported [40]. Vitenet et al. reported that WBC significantly improved health-reported quality of life, evaluated through the changes in

the Medical Outcome Study Short Form-36 (10 sessions over 8 days) [35]. However, the sample size was limited, as only 11 patients underwent WBC and the control group protocol was not described in detail. This was the same for the study of Metzger et al. that described a decreased pain intensity and a short-term pain relief of about 1.5 h after cold application. No control group receiving a regular rehabilitation program could be compared to a group additionally treated with WBC [36]. Therefore, the reduction in pain could probably be due not only to the analgesic effect of the WBC, but also to the effect of the applications carried out in parallel. However, they described some adjustment time before reaching maximum pain relief, in their case after about two weeks (half of the treatment). Interestingly, most patients rated the effect of WBC as not very effective in the context of the overall treatment, perhaps also due to the session conditions (temperature -105°C and 2–3 patients in the chamber). Klemm et al. included patients with standard treatment before and during the study, excluding physical activity as a possible confounder of the reduced level of pain found after WBC treatment, but no control group not undergoing WBC was present [37].

Only Rivera et al. [40] and Klemm et al. [37] investigated the effects of WBC on FIQ, and only Vitenet et al. [35] and Klemm et al. [37] included a follow-up, after 1 and 3 months, respectively, showing that the effects of WBC on pain and disease activity after discontinued treatment were no longer reduced. In addition, Klemm et al. demonstrated that serial WBC (between 6 and 10 sessions in a maximum of 3 weeks) elicited effects for more than 1 month after the end of WBC treatment, then decreasing gradually to null effect after 3 months [37].

Two studies compared the effects of WBC with other classic thermotherapy methods. Kurzeja et al. investigated the effect of thermotherapy with WBC (-110°C) alone compared with mud bath ($+40^{\circ}\text{C}$) and hot air ($+42^{\circ}\text{C}$) combined in the daily shift. Pain intensity was reduced in all groups with no significant differences between groups [38]. However, the pain scores in the WBC group were lower and the patients described a 2-h pain relief after cold exposure.

The abstract of Sundaram mentions that WBC provides better results in association with physiotherapy than with steam therapy. Improvement in pain, general health, fatigue, and sleep are attributed by the author to the systemic response and serotonin levels stimulated by WBC [39]. However, no information about the temperature was mentioned, the sample was not homogeneous in terms of age and gender, and there were no actual data to corroborate the findings and conclusions.

3. Molecular Effects of WBC in FM

The pathogenesis of FM not only includes pain sensitivity, pain inhibition, or pain amplification, but also an imbalance of pro- and anti-inflammatory cytokines, genetic predisposition, and environmental triggers such as mechanical/physical trauma or injury and psychosocial stressors that ultimately leads to pain and impaired pain processing.

There is growing evidence of neuroinflammation in FM. Several pro-inflammatory cytokines, including $\text{TNF-}\alpha$, $\text{IL-1}\beta$, IL-6 , and tumor necrosis factor α ($\text{TNF-}\alpha$), have been found to be elevated in animal models of neuropathic pain and in the cerebrospinal fluid (CSF), peripheral tissues, and blood of patients with chronic neuropathic pain conditions [72]. In addition, pharmacologically lowering or blocking of these pro-inflammatory cytokines has been demonstrated to prevent, reduce, or reverse pain (allodynia and hyperalgesia) in both animal models and clinical studies [73].

Thus, the imbalance of pro- and anti-inflammatory cytokines is assumed to play a role in the induction and maintenance of pain and the occurrence of many of the clinical features of FM (such as swelling, dysesthesia, skin manifestations, fluid retention, and increased levels of fibronectin, which is a tissue marker of endothelial activation) as a result of a neuroinflammatory condition that gives rise to descending pathways that influence predominant symptoms, such as pain, fatigue, and cognitive impairment. In addition, environmental triggers, stress, and emotions are the upstream driving mechanism of neurogenic inflammation in FM [74].

Therefore, the likelihood that FM may have an imbalance in cytokine production and secretion has been confirmed. Ucelyer et al. showed that FM patients have higher serum levels of $\text{IL-1}\alpha$, IL-6 , and IL-8 , and higher plasma levels of IL-8 , compared to controls [75], while two studies of Lubkowska et al. showed how WBC affects the inflammatory status by inducing an imbalance towards the anti-inflammatory side [55][56]. Consecutive sessions of cryotherapy increased levels of IL-6 , which can act both as a pro-inflammatory and anti-inflammatory cytokine, and IL-10 , an anti-inflammatory cytokine, and lowered the $\text{IL-1}\alpha$ levels. Furthermore, WBC appears to improve the oxidative status already after a limited number of sessions, in a dose-dependent way [58][59].

Klemm et al. integrated the clinical effects with the molecular effects of WBC [37]. In parallel with changes in disease activity and pain reduction, patients with FM showed a significantly different response to WBC compared with healthy controls in terms of changes in IL-1 , -6 , -10 , and $\text{TNF-}\alpha$ over time to WBCs. FM patients had higher levels of IL-1 , -6 , -10 , and $\text{TNF-}\alpha$ at baseline compared to healthy subjects. IL-1 , IL-6 , and IL-10 levels decreased significantly after three and

six sessions and stabilized up to three months after discontinued WBC treatment. Interestingly, IL-6 levels returned to baseline after three months only in healthy controls and showed significantly decreased IL-6 levels at each reading point compared to baseline. WBC had no effect on TNF- α levels, neither in FM patients nor in healthy controls.

Therefore, even if the levels of IL-1, IL-6, and IL-10 in FM patients were higher than healthy controls after 6 WBC sessions and 3 months after the last WBC session, their significant alteration confirms the overall beneficial effects of WBC.

4. Gene Expression after WBC in FM

Drynda et al. investigated the changes in gene expression on peripheral blood cells of patients with FM going through a series of three exposures to WBC within three days [32]. One study correlated the reduced pain intensity with transcripts that were found significantly changed already after a single exposure to WBC. The majority of down-regulated transcripts belonged to a group of small nucleolar RNA (SNORD) while the up-regulated transcripts were a few specific genes, such as PBX1, SFRP2, MAP2K3, and SLC25A39. SNORD molecules belong to so-called non-coding RNAs. Emerging evidence has demonstrated that they are involved in various physiological and pathological cellular processes acting as internal signals that control various levels of gene expression. However, the sample size and homogeneity were rather limited, as only 10 patients were studied.

Another study from the same group investigated on a larger cohort of 22 patients the changes in the gene expression of selected genes (CCL4, TGFBR3, CD69, and MAP2K3) identified as significantly regulated in cells from peripheral blood of patients with FM going through a series of three exposures to WBC within three days [31]. The expression levels of CCL4 and CD69, two proteins produced upon activation of T-lymphocytes, reduced significantly after the third exposure compared to baseline. In contrast, the expression of MAP2K3, a protein activated by cytokines and environmental stress in vivo, was found to be up-regulated in 13 patients, while the expression levels in the other 9 patients remained almost unchanged. Interestingly, the changes of gene expression were evident already after the first cold exposure, but reached statistical significance after the third exposure. The down-regulation of TGFBR3, a membrane proteoglycan that often functions as a co-receptor with other TGF- β receptors observed in the pilot study, could not be confirmed in the larger cohort. Unfortunately, both studies are scientific abstracts only and do not provide further speculation or discussion of the results.

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