Research Article

Cryotherapy as Adjunct Treatment for Fibromyalgia

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Abstract

Common symptoms associated with fibromyalgia are chronic widespread pain, fatigue, sleep disturbances, depression, and cognitive dysfunction. Cryotherapy, which is commonly used in sports medicine, is used to alleviate pain and inflammation by exposing the body to cold temperatures maintained at -110°C and below. Recent evidence has shown that cryotherapy has a potential beneficial role in treating fibromyalgia. This review summarizes the unknown etiology of fibromyalgia, first-line treatment options for fibromyalgia, and how cryotherapy can be effective in reducing fibromyalgia symptoms. Cryotherapy might be useful adjunctive treatment but further research is still needed with larger sample sizes.

Keywords: Cryotherapy, fibromyalgia, diagnosis, pain, fatigue, sleep disturbances, depression, cognitive dysfunction, tricyclic antidepressant

1. Introduction

Fibromyalgia (FM) is characterized as chronic musculoskeletal pain with other symptoms such as cognitive dysfunction, sleep disturbances, fatigue, and psychiatric symptoms such as depression [1]. It affects approximately 1-5% of the population worldwide and it is more commonly seen in females [2]. It is still unclear what the pathophysiology is, but it may involve neural over-sensitization, inflammatory cytokines, and gene polymorphism [3].

This causes a diagnostic challenge for physicians because FM has overlapping symptoms with other disease states such as irritable bowel syndrome. Due to the poor quality of life, patients with FM frequently seek medical attention, which leads to increasing healthcare costs for the patient [4]. The

most recent and internationally accepted diagnostic criteria for FM are the American College of Rheumatology (ACR) 2016 Cr (Table 1) and the ACTTION-APS Pain Taxonomy (AAPT) Cr; however, diagnosis can still take about 2.3 years from onset of symptoms [5].

To treat FM, it is recommended to use a multimodal approach with pharmacological and non-pharmacological treatment options. However, compliance is low for long term pharmacological options due to efficacy and/or side effects. Recent evidence shows that cryotherapy, a non-pharmacological option, can be effective in treating symptoms associated with FM.

Table 1: ACR criteria to diagnose fibromyalgia in adults [5]

Fibromyalgia Diagnostic Criteria (FDC)	
Criteria	1. Widespread pain index (WPI)7≥and symptom severity scale (SSS) score >5 or WPI 4-6 and SSS score≥ 9 2. Generalized pain, defined as pain as in at least 4 of 5 regions, is present 3. Symptoms have been present at a similar level for at least 3 months 4. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses

Cryotherapy refers to cold therapy used to relieve pain and inflammation, and recent evidence shows that it has positive effects on depression, memory deficits, and sleep disturbances [6]. Cryotherapy is commonly used in sports medicine, but it has been shown to be effective in other areas such as multiple sclerosis, ankylosing spondylitis, rheumatoid arthritis, and FM [6]. Whole body cryotherapy (WBC) is when a patient undergoes at most a 5-minute interval in a chamber with low temperatures between -110° to -160°C. In the chamber, patients are minimally dressed and are first preconditioned at -60°C for 30 s [6]. In this review, we will discuss the efficacy of cryotherapy on the associated symptoms of FM and discuss other treatment options.

2. Methodology

PubMed and Google Scholar were used to find original and review articles from 1990-2020 regarding cryotherapy as adjunctive treatment for fibromyalgia. Keywords included “cryotherapy,” “fibromyalgia,” “pain,” “depression,” “SNRI,” “tricyclic antidepressants,” “cognitive dysfunction,” “sleep disturbances,” and “fatigue.” Articles that discussed cryotherapy to help treat the symptoms of FM were the primary focus for this review.

3. Disorders associated with FM

3.1 Pain

According to the 2011 International Association for the Study of Pain (IASP) taxonomy, pain is broken into three subtopics: nociceptive, neuropathic, and nociplastic. Nociceptive pain is due to non-neural tissue damage, neuropathic pain is due to somatosensory nervous system damage, and nociplastic pain is caused from an unknown origin [7]. Patients with FM may experience neuropathic pain such as tingling, burning, and prickling sensations similar to diabetic peripheral neuropathy [8]. To treat these sensations, gabapentoinoids are used, even though FM is not considered a neuropathic condition [9].

In FM, pain is classified as nociplastic pain, which is often referred to as central sensitization and originates from altered nociception without tissue or somatosensory damage. In nociplastic pain, there are alterations within the CNS that may cause central excitability and a decrease in central inhibition. Patients with FM often experience diffuse hyperalgesia (heightened sensitivity to pain) and allodynia (experiencing pain in response to a non-painful stimuli) [10].

This can be due to having improper levels of pro- and anti-inflammatory mediators as well as neurotransmitters [6]. These mediators include high levels of cerebrospinal fluid of neurotrophins, interleukin (IL)-6 (induces hyperalgesia), IL-8 (promotes sympathetic pain), and IL-1ra [11]. For nociplastic pain, patients are often prescribed serotonin-noradrenaline reuptake inhibitor (SNRI) and tricyclic antidepressants. [9]

To see if WBC can decrease pain, a study with 100 patients with FM was conducted. Of the 100 patients, 94 were females and 6 were males with an age range between 17-70 years. Half the patients underwent WBC and the other half did not. The 50 patients who underwent WBC had 15 sessions within 3 weeks. Before each session the patients were preconditioned at -60°C for 30 seconds and then at -140°C for 3 minutes. Inside the chamber, patients were told to avoid breath holding, and after each session they had to complete 30 minutes of aerobic exercises.

To evaluate pain, the Visual Analogue Scale (VAS) was used, which is a psychometric response scale to measure the intensity of pain [12]. Before the study, the median VAS score was 90 for both groups. By the end of the study, the VAS scores of the WBC and non-WBC group were near 35 and 65, respectively. The WBC group was statistically significant ($P<0.001$) compared to the non-WBC group [6]

3.2 Depression

Patients with FM may experience depression and potentially WBC can be used to treat it. WBC relieves inflammation and oxidative stress, which can help in the treatment of depression because inflammation is considered one of the causes and oxidative stress markers are increased in depression [13-16]. Inflammatory factors include C reactive protein, tumor necrosis factor alpha, and IL-6.

As mentioned before in Wallace et al, IL-6 is known to cause hyperalgesia. Even though IL-6 is characterized as a pro-inflammatory cytokine, it is also seen in depression and it is known to induce anti-inflammatory mediators such as IL-1ra and IL-10 [17]. In healthy people undergoing WBC, IL-6 and IL-10 increase, and IL-1α and total antioxidant

status (TAS) decrease [18]. In obese patients or patients who have ankylosing spondylitis, an opposite effect occurs where there is a reduction in IL-6. These patients also experience a decrease in CRP, IL-1β, and TNFα [14, 19, 20]. In combination with physical therapy, WBC can decrease oxidative stress markers [21].

A study of 92 patients who were on antidepressants assessed mood, quality of life, and biochemical measures after WBC. The prescribed antidepressants the patients were already on did not change during the study. Some of the exclusion criteria were dementia, suicidal thoughts, and psychosis. To measure the effectiveness of WBC on depression, Beck Depression Inventory-II and HAM-D 17 were used [22]. Both tools use a point system, and based on how many points an individual receives per item tells them how severe their depression is. A lower score indicates a mild depressive episode, whereas a higher score is more severe. Before initiation of the study, 34 patients resigned due to claustrophobia, not having enough time, or fear of WBC.

During the study, 29 patients dropped out because they had undiagnosed hypertension or developed medical conditions such as a cold or flu. After 10 sessions of WBC, 30 patients were in the experimental group (-110°C to -160°C) and 26 patients were in the control group (-50°C). To determine the efficacy of WBC, four assessments were done during the 10 sessions: before the first WBC, after the sixth WBC, after the tenth WBC, and 2 weeks after the tenth WBC. When comparing the first assessment to the fourth assessment, the HAM-D score improved and was statistically significant for the experimental group ($P<0.02$) [16]. According to the Beck Depression Inventory-II, the experimental group was not statistically significantly different from the first assessment to the fourth assessment. However, it did improve from the first assessment to the second assessment and was significant ($P<0.01$) [16]. When compared to the control group, the experimental group improved and was statically significant on the last assessment for sadness ($p<0.002$), crying ($P<0.03$), loss of pleasure ($P<0.02$), loss of interest ($P<0.01$), self-criticalness ($p<0.05$), and indecisiveness ($P<0.03$) [16].

3.3 Cognitive Dysfunction

Mild cognitive impairment (MCI) is seen in patients with FM. It is detrimental to a patient's health because within 2 years a patient will have a 40% risk of developing dementia [23]. MCI can have multiple definitions such as normal cognitive ageing, cognitive impairment with no dementia (CIND), and amnestic MCI. Normal cognitive ageing is impairment based on memory tests, CIND is used for patients who do not meet the criteria for dementia, and amnestic MCI is used for patients who have more memory issues compared to people of the same age [24].

Pro-inflammatory mediators such as cytokines, reactive oxygen species, and nitric oxide are possible causes of neurodegenerative disorders [23]. There is no cure for MCI, but WBC can regulate cytokines and nitric oxide, which may reduce MCI development and slow its progression by suppressing inflammation in the brain. A clinical study was done to see if WBC could improve MCI and early dementia [25].

The screening tools used to assess patients were the Montreal Cognitive Assessment, Test Your Memory (TYM), Verbal Fluency Test (FAS) and the Saint

Louis University Metal Status Examination (SLUMS) [25]. A blood test was also used to test different levels of cytokines, brain derived neurotrophic factor, and nitric oxide at baseline and at the last WBC session. In this study, a total of 28 patients were evaluated in 10 WBC sessions. To be included in the study, patients needed have a score between 20 and 26 for the Montreal Cognitive Assessment test before the first WBC. Of 28 patients, only 21 completed the study because six patients had high blood pressure and one patient had an injury not related to WBC. Upon completion of the study, DemTect ($P<0.05$), TYM ($P<0.0001$), SLUM ($P<0.0001$), and FAS ($P<0.05$) all improved and were statistically significant for cognitive functions. Blood tests showed increased nitric oxide levels in plasma ($P<0.05$), decreased levels of IL-6 ($P<0.05$), decreased levels of IL-10 ($P<0.05$), and increased concentration of brain derived neurotrophic factor ($P<0.05$). The increase in brain derived neurotrophic factor and the decrease in inflammatory cytokines could indicate a neuroprotective effect [25].

3.4 **Sleep Disturbances**

It is estimated that 65% to 99% of people with FM experience poor sleep quality, but it is not considered a pathogenesis of FM [26-28]. Studies have showed that an increase in pain reduces sleep quality and poor sleep can increase pain [29]. When assessed via a polysomnography, patients experienced a greater chance of light sleep stage and shorter sleep duration [30]. This is because there could be disturbances in the rapid eye movement (REM) phase, which could be from heart rate variability (HRV) [31].

The REM phase is the most important sleep phase because it provides relaxation to the muscles and is associated with better mood and cognitive functions [32]. With disturbance of REM, there can be a worsening of associated symptoms in FM such as pain, cognitive function, fatigue, and quality of life[33].Without disturbances, HRV can increase REM and decrease non-REM sleep because there are slow wave sleep episodes, which regulate normal respiratory pattern and have less body movements and arousal [34].

Cold exposure is proposed to have a beneficial effect on the quality of sleep due to the reduction in muscle soreness [35]. In professional basketball players and female swimmers, cryotherapy was shown to promote good sleep quality [36, 37]. A study was conducted involving 22 physically active men to see if a 3 minute WBC can improve sleep quality. Each WBC session was done once per week and the study lasted for two weeks. To assess sleep quality, sleep efficiency and the number of movements on three spatial axes (vertical, horizontal, and perpendicular) were measured. Each participant had to work out for 55 minutes per day and record hours of sleep in a log book. To assess HRV and movements during sleep, each patient wore a heart rate monitor and a wrist actigraph. After each session of WBC in the evening, the number of movements decreased on three spatial axes ($P<0.01$). This means it induced lower motor activity, which results in better sleep quality. After WBC, HRV was unaffected during the first four hours and the remainder of the night. However, within the first 10 minutes of the slow wave sleep episode, there was greater parasympathetic activity, which reveals better sleep quality [38].

3.5 **Fatigue**

There is a great deal of agreement in the literature that fatigue is an important symptom to measure in FM [39]. Commonly used measurement tools are the

Multidimensional Fatigue Inventory (MFI) and the Multidimensional Assessment of Fatigue (MAF) [40, 41]. The MFI is a 20 question scale used to measure fatigue whereas the MAF is a 16 item scale. The MFI measures physical and general fatigue and the MAF measures the impact of fatigue. Fatigue is similar to pain in that it relies on patient reports and there is a lack of effective treatment strategies. In FM, patients will not experience just fatigue, they will also experience other symptoms such as depression, pain, and cognitive dysfunction [42]. In FM and chronic fatigue syndrome, fatigue is broken into peripheral and central fatigue, which are associated with a decrease in muscle contraction and cognitive impairment, respectively [43]. Elevated inflammatory markers are possible explanations for fatigue in FM. In chronic fatigue syndrome, there is an increase in IL-1β, TNF-α, and IL-6 [44].

Recent evidence has shown that cryotherapy can help in fatigue related to FM [45]. The Bettoni et al study described above in the pain section also evaluated the effects of fatigue on a fatigue severity scale (FSS), consisting of 9 items that measure the severity of fatigue and how it affects a person's daily life. Prior to WBC, patients had a score of 58 out of 63 on the FSS. Table 2 lists questions associated with the FSS on a self-reporting scale. After WBC, patients recorded a decrease to a score of 27 ($P<0.0001$). Another study was conducted to evaluate WBC as a treatment for fatigue in multiple sclerosis patients. Patients enrolled (n=72) had an FSS score of >38 and did not use any pharmacological options to treat fatigue such as amantadine or modafinil[45]. These patients had 10 WBC sessions lasting 2-3 minutes and were divided between low and high fatigue based on the FSS. The low fatigue group had a score between 38-42 and the high fatigue group and a score between 48-52. The study concluded that WBC was more impactful in the high fatigue group than in the low fatigue group. However, both groups were statistically significant ($P<0.01$) in reducing physical and psychological of fatigue [45].

Table 2: FSS to distinguish between fatigue and clinical depression [6]

Fatigue Severity Score (FSS)	
1.	My motivation is lower when I am fatigued
2.	Exercise brings on my fatigue
3.	I am easily fatigued
4.	Fatigue interferes with my physical functioning
5.	Fatigue causes frequent problems for me
6.	My fatigue prevents sustained physical functioning
7.	Fatigue interferes with carrying out certain symptoms
8.	Fatigue is among my three most disabling symptoms
9.	Fatigue interferes with my work, family, or social life.

4. Potential FM Management Approaches

4.1 Non-pharmacological Options

In addition to WBC, there are multiple interventions that can be used to treat FM, but the most widely studied are physical exercises and cognitive behavioral therapy (CBT) [46]. In 2017, there were 29 studies from 12 different countries evaluating exercise. There were three sessions of mixed exercises over 14 weeks, which included aerobic, strengthening, or flexibility. The mixed exercise group and control group were evaluated on a scale from 0 to 100. The participants involved were mostly female and they had to work out for 50-60 minutes 3 times a week. At the end of the study, exercise showed improvements in pain, tiredness, stiffness, physical function, and health related quality of life [47] .

CBT has shown positive effects in FM because it reduces pain intensity and emotional distress. CBT works by using techniques to identify distorted beliefs and having the patient participate in behavioral intervention. One of the goals of CBT is not having catastrophizing thoughts, which is assuming the worst possible outcome [48]. Studies have shown that in the short term, physical exercise is better than CBT in treating FM[49]. To evaluate long term effects, a study was conducted comparing CBT and physical exercise. In this randomized parallel trial, 40 female patients diagnosed with FM were either placed in the CBT group (n=21) or exercise group (n=19) for 8 weeks. The exercise group had to work out for 45 minutes 5 times per week and the CBT group underwent behavioral techniques.

All patients had a baseline assessment and were evaluated after 8 weeks, 6 months, and then 1 year. The exercise group showed improvement in the FM impact questionnaire and the bodily pain domain in the Short Form questionnaire (SF-36) after 8 weeks; however, the assessment at 6 months and at 1 year did not show any clinical improvements. Similarly, CBT showed significant improvement in the Fibromyalgia Impact Questionnaire (FIQ) after 8 weeks, but at 6 months and 1 year the clinical values were similar to baseline[50].

4.2 Pharmacological Options

Drugs that are commonly prescribed for FM and can be considered first-line options are duloxetine, milnacipran, amitriptyline, and pregabalin [51]. These medications are the treatment of choice. Their efficacy is measured with the FIQ (Table 3) and health-related quality of life (HRQL) to evaluate pain, depression, fatigue, and sleep quality [51].

Table 3: Tool to assess and evaluate the progress and outcomes of fibromyalgia [51]

Fibromyalgia Impact Questionnaire (FIQ)
1. Do your shopping? 2. Do laundry with a washer and dryer 3. Prepare meals 4. Wash dishes/cooking utensils by hand 5. Vacuum a rug 6. Make a bed 7. Walk several blocks 8. Do yard work 9. Drive a car 10. Climb stairs 11. Of the 7 days in the past week, how many days did you feel good? 12. How many days last week did you miss work including housework because of fibromyalgia? 13. When you worked, how much did pain or other symptoms of your fibromyalgia interfere with your ability to do your work, including house work? 14. How bad has your pain been? 15. How tired have you been? 16. How have you felt when you get up in the morning 17. How bad has your stiffness been? 18. How nervous or anxious have you felt 19. How depressed or blue have you felt

Duloxetine and milnacipran are SNRIs that are used to treat depression. Both are FDA approved drugs for fibromyalgia, and they inhibit pain signals to the CNS by increasing norepinephrine and serotonin. In treating FM, SNRIs like duloxetine are used in lower doses (30 mg) to relieve pain, improve sleep, and lessen fatigue[52]. However, they are not approved by the European Medical Agency because their effects are not as efficacious in treating symptoms of FM [53]. Based on limited clinical trial data, duloxetine and milnacipran have shown improvements in pain, fatigue, depressed mood, and HRQL; however, duloxetine has been shown to be more effective in treating depressive symptoms, whereas milnacipran is more effective in treating fatigue[51]. Amitriptyline, a tricyclic antidepressant, is not an FDA approved drug, but it is used to reduce pain and fatigue in FM. The mechanism of action is inhibition of serotonin and noradrenalin reuptake [54]. Evidence shows that amitriptyline may provide good pain relief but it is effective in a limited number of people; only one of four people treated will experience at least a 50% pain reduction [54]. When compared to nine placebo controlled studies, five studies revealed superiority of amitriptyline in treating pain and four studies revealed superiority on

fatigue [55-62]. The majority of these studies were small with under 40 people selected in the amitriptyline group. Pregabalin is a gabapentoinoid that binds to the voltage gated calcium channel in the CNS via the alpha$_2$delta subunit. It controls the release of excitatory neurotransmitters, glutamate and substance P through the ascending pain pathways, which decreases nociceptive signals [63]. Pregabalin is an FDA-approved drug, and based on clinical results showed improvements in pain and sleep quality, but no significant improvement in fatigue or in depression [51].

To treat other symptoms of FM, a combination therapy of pregabalin and milnacipran was evaluated to see if different mechanisms of action would be efficacious in treating FM. The clinical trial assessed 58 patients based on the VAS, FIQ and the Leeds Sleep Evaluation Questionnaire. In the study, 29 patients received pregabalin and 19 patients received pregabalin and milnacipran. Both groups were started on 150 mg of pregabalin and then gradually increased up to 450 mg per day. In the combination group, 12.5 mg of milnacipran was initially used and was gradually increased to 100 mg per day. The combination therapy showed better improvement in pain and disease impact than monotherapy based on VAS and FIQ, but it was not statistically significant ($P>0.05$)[52]. Duloxetine, milnacipran, amitriptyline, and pregabalin are effective at treating pain in FM, but one medication cannot treat all symptoms associated with FM. Many patients will try these medications, but due to adverse effects or lack of improvement they will not take them for the long term. According to the 2016 FM treatment guidelines of the European League Against Rheumatism (EULAR), using non-pharmacological therapies is recommended first, then if no results are seen, pharmacological treatments are recommended next [52].

5. Future prospective

FM is a difficult disease to treat due to its unknown pathophysiology and lack of reliable biomarkers. New areas of interest such as biological fluids could be the future as indicators for the presence or severity of FM. Studies showed that whole body cryotherapy (WBC) is effective in FM and might lower the burden of FM. The effects of serial WBC are strongest during application and are diminished overtime but with longer-term lowering of certain pro-inflammatory cytokines [64]. Different means of diagnosing FM using cerebrospinal fluid, blood, and saliva have shown miRNA profiles that could be used to diagnose FM, which would eliminate the need for clinical assessment and patient reports [65]. miRNAs act as post-transcriptional regulators and are stable in extreme pH and high temperature and can be analyzed via quantitative polymerase chain reaction; however, drugs could impact these levels. A study with 14 female patients with FM and free from medications were evaluated to analyze the expression of saliva and serum miRNAs. Hsa-miR-10a-5p, hsa-miR-320b, hsa-miR-424-5p, hsa-miR-20a-3p, and hsa-miR-139-5p were miRNAs that were statistically significantly different between the FM group and control group. These miRNAs are related to symptoms of FM such as pain, depression, and mood disorders and may be useful as a potential biomarker of FM [65].

3. Conclusions

Cryotherapy has shown positive effects in treating the associated symptoms of FM, but more research is needed due to the small sample sizes of existing studies. Because current treatment options are

palliative, multidisciplinary approaches are needed because FM has no cure. Non-pharmacological therapies are recommended first and if no improvements are seen, pharmacological treatments along with non-pharmacological interventions are recommended.

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