The effects of microphysiotherapy on quality of life, pain, and serum IL-8 concentration in women with fibromyalgia: A double-blind randomized controlled trial.

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Abstract

Fibromyalgia (FM) is a chronic painful syndrome associated with persistent pain and emotional symptoms such as depression and anxiety. Microphysiotherapy is a French technique of manual therapy that identifies the primary cause of a disease or symptom. The study consisted of an intervention group (MG) treated with microphysiotherapy (n = 20) and a placebo group (PG) treated with placebo intervention (n = 19). Patients treated with microphysiotherapy have shown improvement on quality of life, especially regarding pain, fatigue, morning tiredness and depression. Serum IL-8 concentration did not alter significantly between and within groups.

Keywords: Chronic pain. Fibromyalgia. Integrative Therapies. Physiotherapy. Rehabilitation.

1. Introduction

Fibromyalgia (FM) is an idiopathic chronic pain syndrome (Senna, 2004; Brietzke, 2019; Vitorino and Prado, 2004; Lee et al, 2017; Clauw, 2015) that predominantly affects females (Häuser et al., 2014) aged 20 to 55 years (Heidari et al, 2017), approximately. Individuals with FM usually present persistent pain for more than three months, with depression and anxiety (Wolf, 2017). FM causes secondary problems, such as limitations in activities of daily living, which have been associated with biopsychosocial disorders. Even so, the etiology and pathophysiological mechanisms of FM are unknown, so scientific research on this subject becomes important (Junior et al., 2012).

FM is a chronic disease that symptoms include hyperalgesia, fatigue, pain, sleep disorders and anxiety that are related to increased inflammatory cytokines (Rodriguez-Pintó et al., 2014; Kadetoff et al., 2012) that mediate changes in the hypothalamus axis. adrenal-pituitary gland (HPA) (Bradley, 2009; Tak et. al., 2011; Savino et al., 2015; Malek et al., 2015; Gupta and Morley, 2011).

Studies show that interleukin 8 (IL-8), whose release is induced by substance P (Xiao et. al., 2013), is increased in the blood of individuals with FM (Xiao et al., 2013; Bote et al., 2013) when compared to healthy individuals (Ortega et al, 2009; Bote et al, 2013), regardless of the association with depressive symptoms (Aderka et al, 1992), demonstrating the occurrence of chronic inflammatory disease (Ribeiro et al, 2016). Increased concentrations of proinflammatory cytokines, such as IL-8, play a role in pain induction and maintenance (Üçeyler and Sommer, 2008) in FM (Bote et. al., 2013), which sometimes have poor quality of life (Clauw, 2015).

Although several pharmacological therapies are used to treat FM, their use has been questioned, as they have little effectiveness and many side effects (Braz, et. al., 2011). Thus, the use of physical therapy has gained space in the treatment of FM, since they have had superior effect to pharmacological therapies and not producing side effects. In this sense, we highlight the microphysiotherapy, a physical therapy technique of manual therapy, which has been growing in Brazil due to the effects observed in several diseases (Salgado, 2013), especially in the emotional background disorders, because the microphysiotherapy acts so much on the somatic aspects as emotional (Schorne, 2015).

Its creators in France have conducted several pilot studies with microphysiotherapy since its development and refinement. It has been observed in several countries and even in Brazil a growing number of publications with this theme. More specifically in the treatment of pain and quality of life, research with microphysiotherapy has received more attention. Pereira et al. (2014) demonstrated in an uncontrolled pilot study that microphysiotherapy increases the quality of life of individuals with FM. In addition, Baconnier et al. (2016) conducted a double-blind randomized controlled trial and verified the benefits of microtherapy in post-traumatic neck pain. They observed that only the group treated with microphysiotherapy presented pain reduction and increased amplitude in neck flexion and extension.

In this sense, the scientific relevance of the proposal was to demonstrate the effects of a microphysiotherapy protocol aimed at increasing the quality of life in individuals with FM. Additionally, the present study investigated the hypothesis that microphysiotherapy could influence pain and serum IL-8 concentration in women with

fibromyalgia. Thus, a randomized placebo-controlled clinical trial was conducted to answer the following research question: What are the effects of microphysiotherapy on quality of life and serum IL-8 concentration in women with fibromyalgia?

2. Material and Methods

2.1 Participants

Female patients with a medical diagnosis of FM (between 34 and 75 years old) were selected at the Physical Therapy Clinic of the University of Southern Santa Catarina (UNISUL), Brazil. All participants met the American College of Rheumatology 2010 classification criteria for fibromyalgia.

Participants with the following criteria were excluded: carriers of immunosuppressive, cancer, infectious, untreated cardiovascular, renal, hepatic, gastrointestinal or psychiatric disorders, use of anti-inflammatory drugs or drugs that affect the inflammatory process (before and after one week of blood collection), pregnant or lactating women, degenerative changes in the spine, motor deficient disc hernias, postoperative spine or rheumatic diseases. Inclusion criteria were: women living in Greater Florianópolis aged 30 to 75 years, with a clinical diagnosis of FM. All participants were advised not to engage in any other regular physical activity, only to maintain the usual ones (physiotherapy, water exercises, acupuncture, etc.) and had to sign an Informed Consent Form (ICF).

Thirty-nine participants were randomly allocated (randomized by Research Randomizer, version 4.0, available at http://www.randomizer.org/) into two groups: (IG) intervention group (n = 20), who received treatment with microphysiotherapy, and (CG) control group (n = 19) receiving placebo treatment. The evaluators and the patients were blinded to the groups.

For the sample calculation a confidence interval of 95% was used; 10% increase for possible follow-up losses; calculations made from the unpaired sample equation for

quantitative variables. To calculate the sample, the following equation was used: n = Zc2 x 2 σ/ (đ) 2.

2.2. Procedures

This study was approved by the Research Ethics Committee of UNISUL (CEP-Unisul) under the number CAAE: 03393318.0.0000.5369 with the opinion number: 3.086.439 and registered in trialsclinicos.gov.br (Brazilian Registry of Clinical Trials [ReBEC]) (RBR - 2p8rrh). Individuals, when invited to participate in the research, obtained knowledge of all study objectives and procedures, which were available in the informed consent form.

After recruitment, participants underwent baseline pain assessments by the Visual Analog Scale (VAS) and quality of life through the FIQ, followed by the first session of microphysiotherapy and evaluated again after 45 days. The second session of microphysiotherapy was performed 45 days after the first and similarly, the participants were submitted to VAS and FIQ evaluations. Blood samples were taken at the UNISUL Experimental Neuroscience Laboratory (LaNex). The collections were performed pre (0 day) and post intervention (after 60 days) between 7:00 and 9:00 hours with participants in a 12-hour fasting. 10 ml of blood was taken from the cubital vein of each participant.

2.3 Microphysiotherapy treatment

Two physiotherapists trained to the MKE (last level) level of microphysiotherapy conducted all sessions. Two sessions of microphysiotherapy were performed, lasting

from 30 to 45min. between the two sessions there were 45 days apart. In each session with the patient lying on the stretcher, the physiotherapist performed micropalpations to identify the etiology and stimulate body self-regulation. For this, the physiotherapist used both hands to perform small movements of approach and light separation in different positions in the region of interest. Based on the depth of palpation and its location in the body, the physiotherapist realized whether the vital rhythm of the underlying structures was disturbed. The microphysiotherapy performed was global. The treatment protocol included basic treatment (up to the new enhancement module 3 - NP3) as well as controls and corrections to the advanced levels (P3, P4, P5 and P6). In each session of microphysiotherapy were recorded the etiologies, the symptoms, as well as the corrections of each patient.

2.4 Placebo group

The control group underwent two sessions, 45 days apart, with an approach called “fake microphysiotherapy” (placebo), simulated over the same period of time, by the same physiotherapists who underwent treatment with the microphysiotherapy. During the simulated treatment, a diagnostic and therapeutic phase was imitated by a gentle massage in random body regions, maintaining the softness of the touch, but uncertainly.

2.5 Measurements

2.5.1 Primary outcome measures

2.5.1.1 Visual Analog Scale (VAS)

Pain was assessed by the Visual Analog Scale (VAS), which consists of a horizontal line 10 centimeters long, numbered from 0 to 10, marked on one end with the classification “no pain” and on the other with the classification “pain unbearable". The patients performed a marking with a dash at the point that represented the intensity of their pain (Galvão and Silva, 2005). The researchers who applied and tabulated VAS results were blinded.

2.5.2 Secondary outcome measures

2.5.2.1. Fibromyalgia Impact Questionnaire (FIQ)

The impact caused by FM on the quality of life of these individuals was measured using the FIQ - Fibromyalgia Impact Questionnaire, which is designed to measure the health status components that are most affected by FM (Wepner, 2014), which was used the portuguese version (Marques et. al., 2006). It is divided into a functional subscale in question 1, which is composed of 11 functional items, questions 2 and 3 report the number of days feeling good (range 0-7) and the number of days unable to work, which included housework (range 0-7). Questions 4 to 10 are horizontal linear scales in which the rate of patients difficulty in doing their work, the level of pain, fatigue, tiredness, morning stiffness, anxiety, and depression (range 0-10) (Marques et al, 2006). Total FIQ score ranges from 0 to 100 points, with a higher score associated with

greater functional impairment and symptoms (Segura-Jimenez et al, 2019; Salgado et al., 2019).

2.5.2.2 Serum IL-8 concentration analysis

The participants' peripheral blood was collected in 10 ml syringes (SR lot: 420 I mark) and 0.80 x 25mm needle (SR Lot 5292198 mark) and placed in 2.0 ml clear K30-1020 centrifuge microtubes. The blood is centrifuged at 5000 rpm for 5 minutes and the serum removed in a sterile environment and stored in microcentrifuge tubes, stored in a freezer at -80ºC (Mendieta et al, 2016). Serum IL-8 concentration analysis was performed by the enzyme-linked immunosorbent assay (ELISA) method using the DuoSet ELISA (R&D Systems, Minnesota, MN, USA) human kit, with sensitivity between 31, 3 pg / ml to 2000 pg / ml. A Perlong model DNM-9602 microplate reader produced in Najing, China took the readings. Adjusted to 450 nanometers (nm) and corrected (substring) wavelength read at 550 nm and values expressed in pg / ml (Mendieta et. al., 2016).

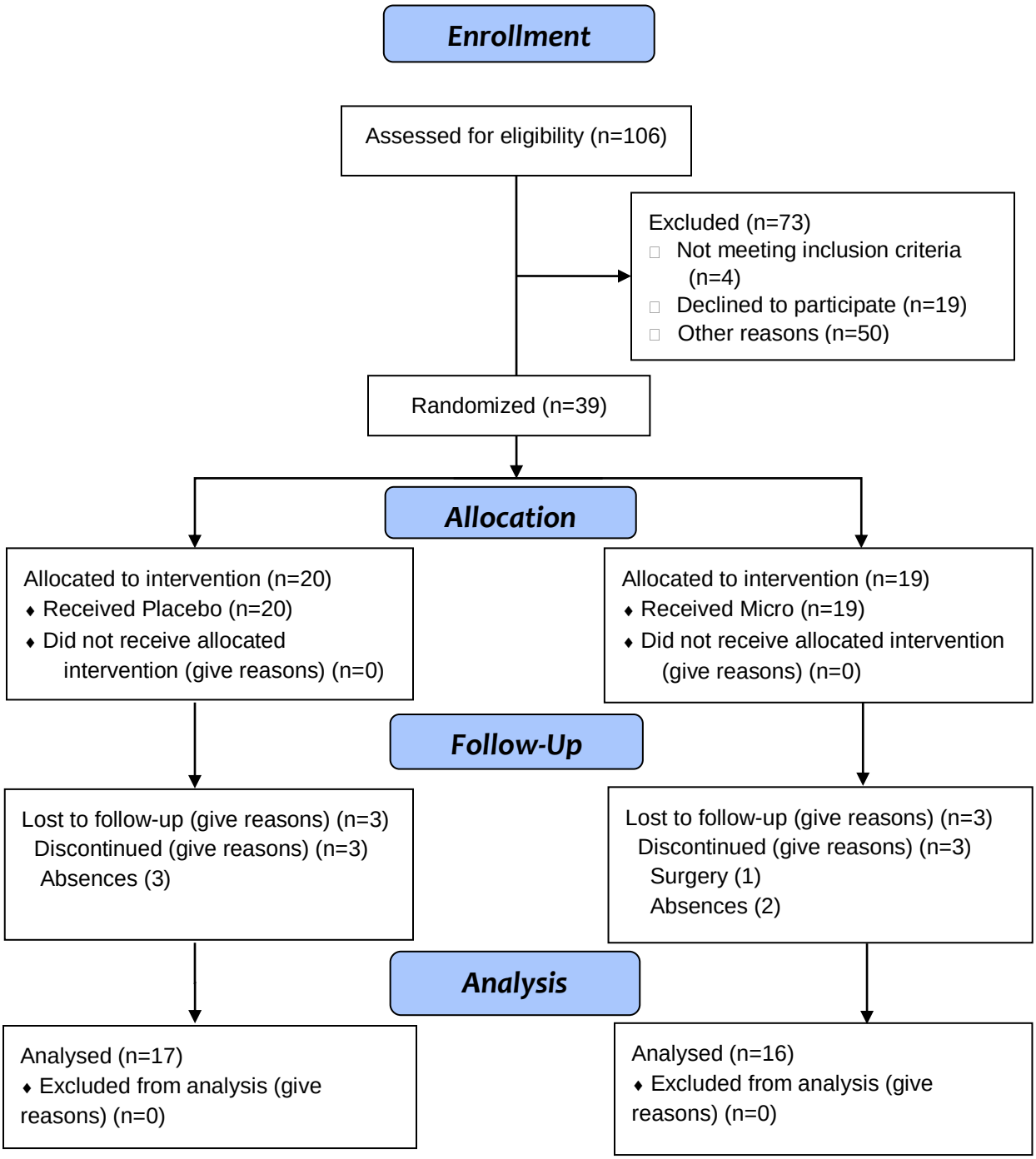
2.6. Statistical analysis

The results were analyzed using the Graph Pad Prism® software (v. 6.0). Initially, data distribution was evaluated by the Shapiro-Wilk test. Thus, the results were presented as mean ± standard error of the mean. Parametric data were compared using two-way analysis of variance (ANOVA) followed by the Bonferroni test. Values less than 0.05 were considered statistically used.

3. Results

3.1 Demographic and clinical characteristics of the subjects

In the present study, 106 women with a clinical diagnosis of fibromyalgia were selected; 73 met the exclusion criteria; therefore 39 were randomly allocated by randomization into two groups: placebo (n = 19) and microphysiotherapy (n = 20). During follow-up there were 6 losses, 3 women in the placebo group (2 dropouts and 1 surgery) and 3 women in the microphysiotherapy group. Therefore, 33 women (84.6%) completed the study. Exclusion criteria are shown in figure 1.


Enrollment
Assessed for eligibility (n=106)
Excluded (n=73)
Not meeting inclusion criteria (n=4)
Declined to participate (n=19)
Other reasons (n=50)
Randomized (n=39)
Allocation
Allocated to intervention (n=20)
Received Placebo (n=20)
Did not receive allocated intervention (give reasons) (n=0)
Allocated to intervention (n=19)
Received Micro (n=19)
Did not receive allocated intervention (give reasons) (n=0)
Follow-Up
Lost to follow-up (give reasons) (n=3)
Discontinued (give reasons) (n=3)
Absences (3)
Lost to follow-up (give reasons) (n=3)
Discontinued (give reasons) (n=3)
Surgery (1)
Absences (2)
Analysis
Analysed (n=17)
Excluded from analysis (give reasons) (n=0)
Analysed (n=16)
Excluded from analysis (give reasons) (n=0)

According to table 1, the mean age was 52 years for GP and 55 years for GM, with no difference between groups (p = 0.36). Regarding the body mass index (BMI), the GP presented 28.1 and the GM 30.03 (p = 0.28). Regarding the time of diagnosis of fibromyalgia, the GP was 6.9 years old and the GM was 7.3 years old (p = 0.82). In the GP, 6 women practiced physical activity regularly, while in the GM only 8 practiced. The number of smokers was 3 in GP and 1 in GM. Regarding the use of analgesics, 9 participants used it in GP while 6 participants did it in GM. In GP, 4 participants had a history of anxiety and in GM 3 participants; Regarding the history of depression, 7 presented it in the GP and 5 in the GM. From the GP, 7 participants were taking active drugs in the CNS, such as selective serotonin reuptake inhibitors (SSRIs), while 5 were in the GM. Regarding the history of chronic diseases, in GP 7 they presented hypertension and 2 type II diabetes, while in GM 5 they presented hypertension and 2 type II diabetes.

Table 1. Epidemiological and clinical characteristics at baseline, according to the treatment group, values are given as the mean (SD).

Characteristics	**Placebo group (n=17)**	**Micro group (n=16)**	***p-value***
Age (years)	52.0 (9.22)	55.25 (11.02)	0.364
Body mass index (Kg/m^2)	28.1 (4.17)	30.03 (6.03)	0.289
Time of fibromyalgia diagnosis (years)	6.93 (4.97)	7.35 (5.28)	0.825
Physical activity	6/11	8/8	
Smoking (yes/no)	3/14	1/15	
Analgesic medication in use (yes/no)	9/8	6/10	
History of anxiety use (yes/no)	4/13	3/13	
History of depression disorders use (yes/no)	7/10	5/11	
Use drug active on the nervous system (yes/no)**	7/10	5/11	
Selective Serotonin Reuptake Inhibitor in use (yes/no)	7/10	5/11	
History of chronic disease (yes/no)	9/8	7/9	
Hypertension (yes/no)	7/10	5/12	
Type 2 Diabetes Mellitus (yes/no)	2/15	2/14	
Visual Analog Scale (VAS)	8.0 (1.54)	7.8 (1.33)	0.987
Fibromyalgia Impact Questionnaire (FIQ)	65.39 (7.40)	61.69 (10.90)	0.995
Physical Impairment	3.99 (0.16)	3.59 (0.21)	0.996
Feel Good	6.31 (2.0)	6.48 (0.63)	0.739
Work Missed	3.34 (0.15)	3.68 (0.96)	0.996
Difficult to work	6.92 (1.85)	6.60 (1.33)	0.816
Pain	7.59 (0.73)	7.24 (1.23)	0.999
Fatigue	7.58 (0.74)	7.07 (1.78)	0.994
Morning tiredness	7.15 (0.86)	6.81 (1.48)	0.999
Stiffness	7.59 (0.72)	6.62 (0.85)	0.733
Anxiety	7.86 (0.27)	6.97 (2.19)	0.932
Depression	7.0 (0.49)	6.58 (2.13)	0.834
serum IL-8 levels	5.70 (0.36)	4.45 (0.53)	0.508

The results presented in Figure 1 show that VAS scores do not statistically differ in between pre- and post-intervention periods of the intergroup. Interestingly, intragroup analysis demonstrates that the Micro-physiotherapy group significantly improved (Maximum inhibition 26±10%) the VAS score in the post intervention evaluation decreasing significantly (p = 0.0159), with a lower VAS score in comparison to placebo group.

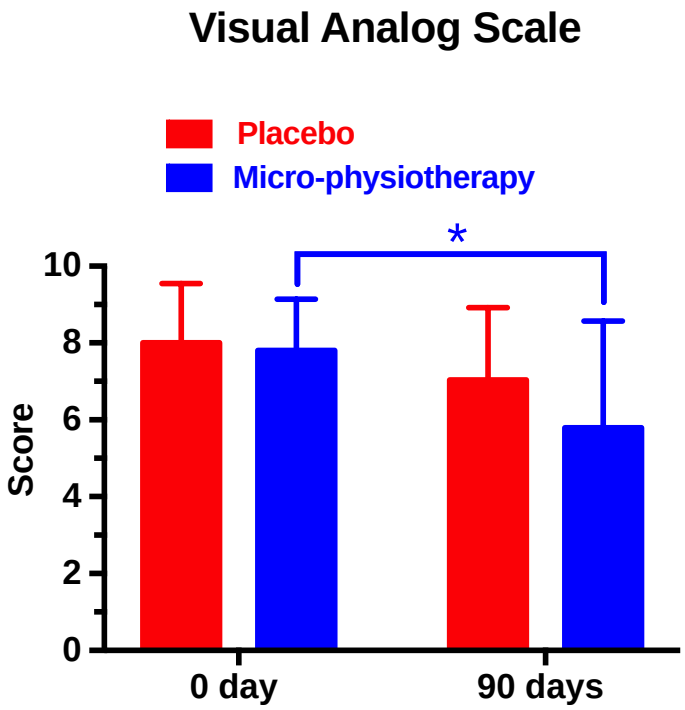
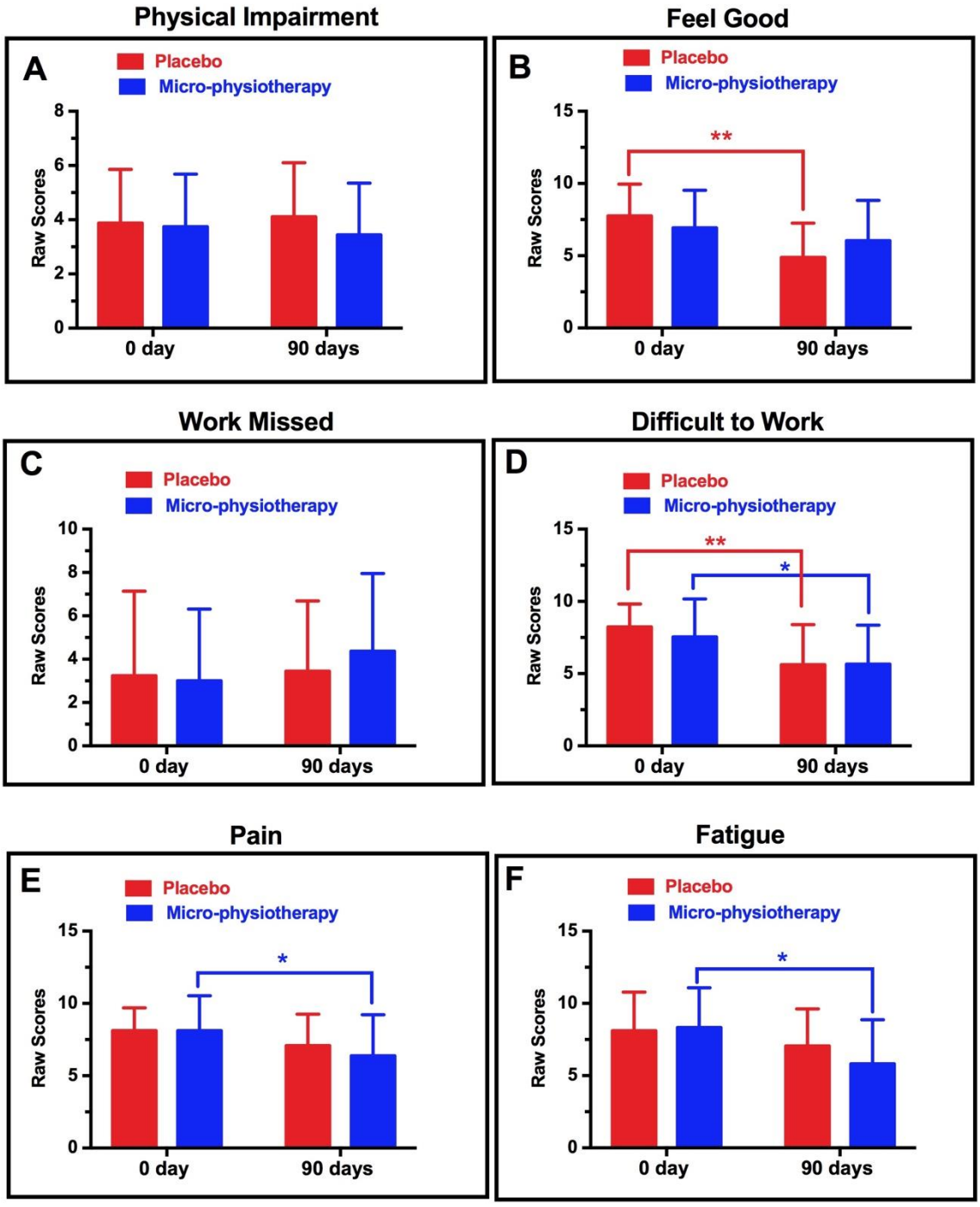


Figure 2. Effects of the micro-physiotherapy on pain assessed through the visual analogue scale (VAS). Two-way analysis of variance followed by Bonferroni post hoc test. *p < 0.05.

As illustrated in Figure 3, it is observed that treatment with microphysiotherapy had a positive effect on aspects related to difficulty in working (panel D, p = 0.042), pain (panel E, p = 0.044), fatigue (panel F, p = 0.013), morning tiredness (panel G, p = 0.031), anxiety (panel I, p = 0.000), depression (panel J, p = 0.002) and total score

(panel K, p = 0.011) in the intragroup analysis. In the intergroup analysis, the treatment with microphysiotherapy was superior to the placebo group only in the anxiety aspect (panel I, p = 0.016). In addition, only the placebo group showed improvement in feeling good (panel B, p = 0.002), but did not differ from the microphysiotherapy group 90 days after randomization (p> 0.999). Finally, the groups showed no statistical difference in the functional capacity (panel A, p = 0.631), work absences (panel C, p = 0.884) and stiffness (panel H, p = 0.479) aspects when analyzed 90 days after randomization.


Physical Impairment
A
Placebo
Micro-physiotherapy
Raw Scores
0
2
4
6
8
0 day
90 days
Feel Good
B
Placebo
Micro-physiotherapy
**
Raw Scores
0
5
10
15
0 day
90 days
Work Missed
C
Placebo
Micro-physiotherapy
Raw Scores
0
2
4
6
8
10
0 day
90 days
Difficult to Work
D
Placebo
Micro-physiotherapy
**
*
Raw Scores
0
5
10
15
0 day
90 days
Pain
E
Placebo
Micro-physiotherapy
*
Raw Scores
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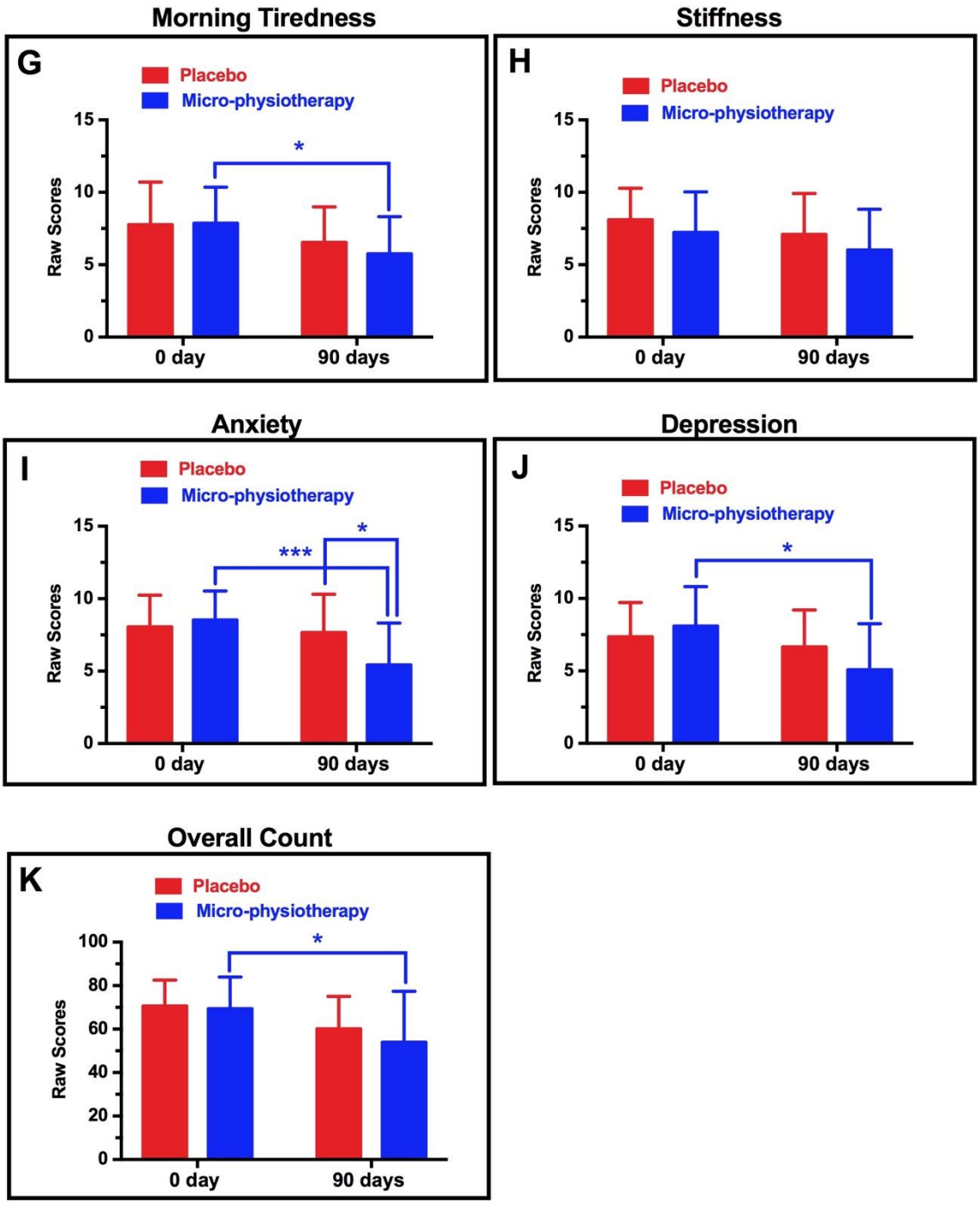

Figure 3. Effects of the micro-physiotherapy on Fibromyalgia Impact Questionnaire (FIQ). Physical impairment (panel A), Feel good (panel B). Work missed (panel C), Difficult to work (panel D), Pain (panel E), Fatigue (panel F), Morning Tiredness (panel G), Stiffness (panel H), Anxiety (panel I), Depression (panel J), Overall count (panel K).

Figure 4 shows that there was no significant difference between the groups analyzed, either before (p = 0.508) treatment at time 0 day or 60 days (p = 0.337) after the randomization of the groups.

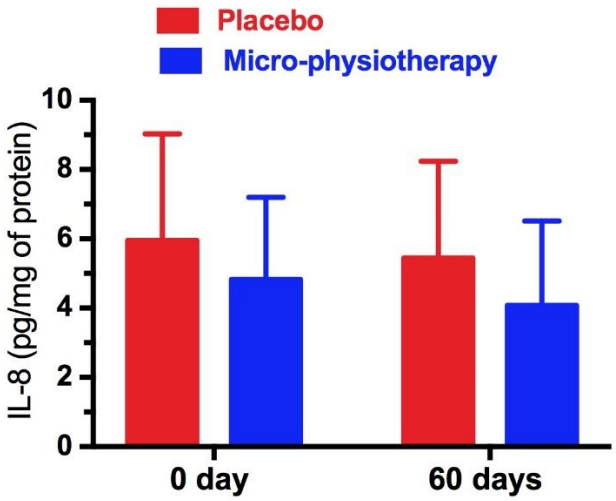

Figure 4. Serum IL-8 concentration.

4. Discussion

The present study aimed to evaluate the effects of microphysiotherapy on pain, IL-8 serum concentration and improvement in quality of life. Microphysiotherapy treatment was able to reduce pain and improve quality of life, but did not influence serum IL-8 concentrations in women with fibromyalgia.

The complexity of studies with the population suffering from FM is partly due to the variability of its clinical manifestation, such as severe diffuse pain, deficit in pain modulation mechanisms, mood and sleep disorders, digestive disorders, cognitive symptoms, fatigue among others. Of these clinical manifestations, pain is the main complaint of patients (Clauw, 2015). Here we observe that both groups of fibromyalgia patients had high levels of pain (8.0 on VAS) before the interventions. These results strengthen the clinical diagnosis of FM of patients in this research and corroborate the literature showing similar levels of pain in fibromyalgic patients (Zhou et al., 2010).

In addition, we demonstrated that treatment with microphysiotherapy, but not placebo, decreased the pain score of FM patients ninety days after the first session. Because no study has yet evaluated the effect of microphysiotherapy treatment on the pain of patients with FM, it is difficult to make a direct comparison with previous studies. However, this observed effect can be discussed and justified based on studies that have shown other effects with microtherapy therapy but that indirectly influence the pain threshold.

In this regard, it was demonstrated in a double-blind study of 61 patients with irritable bowel syndrome (IBS) randomized to two sessions of either microtherapy or sham (placebo) that treatment with microtherapy was superior to sham in reducing the

presence and severity of symptoms, such as abdominal pain, after the first session, being maintained after the second session, although without additional gains (Grosjean et al., 2017). Another interesting study with microphysiotherapy treatment was conducted with patients with cervicbrachialgia. In that randomized controlled trial, the authors showed that treatment with microphysiotherapy was effective in reducing pain (by more than 50%) and restoring the range of motion of flexion and extension of the neck following acute cervical trauma. Effect not observed in the control group (Baconnier et al., 2016). A study with FM patients evaluated the effect of microphysiotherapy treatment on heart rate variability, which is a functional and noninvasive predictor of the autonomic nervous system. The authors submitted 15 individuals of both sexes aged 35 to 40 years with FM to 2 sessions of microphysiotherapy, with an interval of 45 days between sessions. Microphysiotherapy treatment increased sympathetic autonomic nervous system (ANS) activity (Pereira et al., 2014). In most chronic pain conditions an increased and sustained activity of the SNAs is synonymous with pain. However, in those patients who did not present increased SNA activity at baseline conditions, it is expected that this increase induced by the treatment with microphysiotherapy is beneficial to the body and may cause a stimulus to adapt to a new environment, leaving of the pain cycle

Additionally, the role of the neuroimmune endocrine system in the pathophysiology of FM has been hypothesized, thus suggesting an inflammatory disease (Van West and Maes, 2001). Thus, it has been shown that women with FM have a higher serum IL-8 concentration when compared to their healthy peers (Ortega et al., 2009; Mendieta et al. 2016). In this sense, IL-8 induces changes in HPA axis

activity (Elenkov et al., 2005) by altering SNA activity causing a disturbance in the body's protection against SNA-mediated inflammatory cytokine overproduction (Elenkov et al. 2005; Besedovsky and del Rey, 2007). In addition, IL-8 interacts with beta-adrenergic receptors in the SNAs (Kadetoff et al., 2012; Cunha et al., 1991) altering sleep and causing mechanical allodynia (Rodriguez-Pinto et al., 2014).

In the present study, we found high serum IL-8 values (5.8 pg / ml) similar to those found by other authors (6.0 pg / ml) (Mendieta et al., 2016). However, unlike the literature, we found no difference between the groups of healthy and FM individuals (data not shown). Serum dosages of IL-8 concentrations are highly variable and researchers have associated this difference with inclusion criteria and the method of analysis, as reviewed by Uçeyler et al. (2011). Since no statistical difference was found between healthy and FM subjects in the present study, no statistical difference was observed between the groups of FM individuals treated with either microphysiotherapy or placebo.

This finding is justified by the fact that with the microphysiotherapy technique the therapist stimulates the body to reestablish homeostasis (Salgado, 2013). Thus, it is hypothesized that since serum IL-8 concentrations are similar between healthy individuals and individuals with the disease, it is understood that the body of the research subjects were already at homeostasis in relation to serum IL-8 concentration. 8 and that this inflammatory mediator was probably not the main substance mediating FM symptoms. Thus, probably in these individuals with FM the impact of the disease on quality of life and observed symptoms may be due to other inflammatory and neurotrophic mediators already described as IL-6, TNF, BDNF or S-100beta (Stefani et

al., 2019; Mendieta et al., 2016). In this sense, it is suggested for future the blood evaluation of these mediators.

Being a multifactorial disease, questionnaires have been used to more objectively evaluate the subjective symptoms of FM, such as pain, anxiety, depression, among others; strengthening the diagnosis and assisting in the treatment (Marques et al., 2006). The FIQ is the most widely used instrument for assessing the impact of FM and has been translated into several languages such as: Hebrew (Buskila, 1996), German (Offenbaecher, Waltz, 2000), Turkish (Sarmer, Ergin, Yavuzer, 2000), Korean (Kim et al, 2002), Spanish (García et al, 2016), Italian (Sarzi et al, 2003) and French (Perrot, 2003). To assess quality of life in the present study, the Brazilian version of FIQ was used. This questionnaire has also been widely used because it is a tool that is easy to understand and apply; valid and reliable measure of functional capacity and health status of Brazilian individuals with FM. The FIQ consists of issues related to functional capacity, professional status, psychological disorders and physical symptoms. It consists of 19 questions, organized into 10 items. The higher the score, the greater the impact of fibromyalgia on quality of life (Marques et al., 2006).Specifically in the FIQ it was found that the treatment with the microphysiotherapy was able to have a positive impact on women with FM, since it decreased the scores related to difficulty working, pain, fatigue, morning tiredness, anxiety, depression and even even the total score when analyzed before and after treatment.

Interestingly, treatment with microphysiotherapy decreased anxiety and was statistically different from the Placebo group ninety days after randomization. In addition, in the intergroup analysis, treatment with microphysiotherapy was superior to

the placebo group only in the anxiety aspect. Finally, the groups showed no statistical difference in the functional capacity, work absences and rigidity aspects when analyzed 90 days after randomization. Microphysiotherapy treatment, besides reducing pain, was also able to improve aspects related to depression and anxiety that are closely related to the ability of microphysiotherapy to modulate brain regions responsible for limbic system modulation (Salgado, 2013). As there are no previous studies showing the effect of microphysiotherapy on emotional aspects, our research stands out as being the first study to show that treatment with microphysiotherapy reduces the impact of FM on patients mainly by reducing pain, anxiety and depression.

In conclusion, our study showed that treatment with microphysiotherapy was effective in reducing pain and improving quality of life, but did not alter serum IL-8 concentration in women with FM.

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