ClinicalTrials.gov protocol

A 9-week program of supervised occlusive aerobic training in people with fibromyalgia in a hospital setting, and its impact on blood/plasma variables, quality of life and functional autonomy.

06/06/2023

1. Identification of the study

Study ID

PROTOCOL Code: 1441-23

Official title

A 9-week program of supervised occlusive aerobic training in people with fibromyalgia in a hospital setting, and its impact on blood/plasma variables, quality of life and functional autonomy.

Secondary ID

Code 0560-N-22 Andalusian Biomedical Research Ethics Portal (PEIBA). Junta de Andalucía. Government of Spain.

Type of study

Interventional (clinical trial).

2. Study status

Completed.

Date of authorization: Portal de ética de la investigación biomédica de Andalucía (PEIBA). Junta de Andalucía, Spain, June 2022.

Recruitment and closure date: September 2022 to February 2023.

Pre-evaluation date: February 2023

Intervention period date: February to April 2023.

Date of final evaluations: April/May 2023ia artificial

3. Sponsor/collaborators

Responsible for the study

Sponsor-investigator

Researcher information

José Carlos Rodríguez Bautista. Predoctoral researcher at Pablo de Olavide University, Seville (Spain). Department of Physical Activity and Sport Sciences.

Collaborators

- Pablo de Olavide University, Seville. Spain. Physical and Sports Performance Research Center.
- Nuestra Señora de Valme Hospital, Seville. Spain. Internal Medicine Consultation.
- Santa Angela de la Cruz Hospital, Seville. Spain. Internal medicine and rheumatology consultation.
- Andalusian Center of Developmental Biology (CABD), Pablo de Olavide University, Seville. Seville, Spain.

4. Supervision.

The device used for the performance of the intervention period belongs to class I with general regulation for the performance of occlusive training and is exempt to section 510 (k) with LDE code and regulation 21 CFR 870.1875 according to FDA regulation. No product has been exported from the USA.

The study has been reviewed and approved by the review board of the Virgen Macarena and Virgen del Rocío University Hospitals with code 0560-N-22. Biomedical Research Ethics Committee of the Junta de Andalucía, Seville. Spain.

Composition of the review board

Presidente	Dr. Víctor Sánchez Margalet	Esp. Bioquímica Clínica (H.U. Virgen Macarena)
Vicepresidente	Dra. Mª Dolores Jiménez Hernández	Esp. Neurología (H.U. Virgen del Rocío)
Secretario Técnico	D. Carlos García Pérez	Ldo. Administración Dirección de Empresas (Fund. Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla – FISEVI)
Vocales	D. Gabriel Ramírez Soto	Esp. Farmacia Hospitalaria (H.U. Virgen Macarena)
	Dª. Mª Eugenia Acosta Mosquera	Enfermería (H.U. Virgen Macarena)
	Dr. Enrique Calderón Sandubete	Esp. Medicina Interna (H.U. Virgen del Rocío)
	Dra. Cristina Pichardo Guerrero	Responsable Animalario (Instituto de Biomedicina de Sevilla – IBIS)
	Dr. Javier Vitorica Ferrández	Esp. Bioquímica Clínica (Instituto de Biomedicina de Sevilla – IBIS)
	Dr. Enrique de Álava Casado	Esp. Anatomía Patológica (H.U. Virgen del Rocío)
	Dª. Eva Mª Delgado Cuesta	Esp. Farmacia Atención Primaria (DSAP Sevilla Norte-Aljarafe)
	Dª. Angela Cejudo López	Enfermería (DSAP Sevilla)
	Dr. Amancio Carnero Moya	Esp. Biología Molecular (Instituto de Biomedicina de Sevilla – IBIS)
	Dr. Luis Gabriel Luque Romero	Esp. Medicina Familiar (DSAP Sevilla Norte-Aljarafe)
	Dra. Mª Pilar Guadix Martín	Esp. Ginecología y Obstetricia (H.U. Virgen Macarena)
	Dr. Antonio Pérez Pérez	Esp. Bioquímica Clínica (H.U. Virgen Macarena)
	Dr. José Sala Turrens	Esp. Documentación Clínica (H.U. Virgen Macarena)
	Dra. Mª José Carbonero Celis	Esp. Pediatría (H.U. Virgen del Rocío)
	Dª. Mª Esperanza Gallego Calvente	Lda. Derecho (Servicio Andaluz de Salud)
	Dra. Ana Melcón de Dios	Esp. Farmacología Clínica (H.U. Virgen Macarena)
	D. Adolfo Barragán García	Esp. Protección de Datos (H.U. Virgen Macarena)
	Dra. Mercedes Delgado Valverde	Esp. Microbiología (H.U. Virgen Macarena)
	Dª. Sandra Leal González	Lda. Ingeniería Industrial Superior (H.U. Virgen del Rocío)
	Dra. Teresa Molina López	Esp. Farmacia Atención Primaria (DSAP Sevilla)
	Dª. Adriana Rivera Sequeiros	Enfermería (H.U. Virgen Macarena)
	Dr. José Antonio Sánchez Alcazar	Esp. Bioquímica Clínica (Universidad Pablo de Olavide)
	Dª. Regina Sandra Benavente Cantalejo	Lda. Farmacia (Servicio Andaluz de Salud)

Board contact

CEI de los Hospitales Universitarios Virgen Macarena - Virgen del Rocío de Sevilla Avda. Dr. Fedriani, 3 - Unidad de Investigación 2ª planta Sevilla 41071 Sevilla Spain. Tel. +34955008074 Fax. +34955008015 E-mail administracion.eecc.hvm.sspa@juntadeandalucia.es

Committee

The committee monitored protocol data to ensure the feasibility, safety and efficacy of the study with additional recommendations and requirements prior to approval.

5.6.7.8.9 Description of the study.

Summary

Fibromyalgia disease is characterized by a symptomatology that, in many cases, is diffuse and difficult to quantify. Among its most notable symptoms at the physiological level, both peripheral and central, the following should be highlighted. Lower strength production with risk of dynapenia, Latorre-Román, P. Á et al., (2015), low muscular endurance with possible alterations in muscle fiber typology Bonaterra, G. A et al., (2016), lower maximum oxygen consumption (Vo2max), with difficulties in obtaining the same due, in large part, to the problem of achieving maximum effort in this type of person, Valim, V et al., (2002); Bardal, E. M et al., (2013). This can be explained by a decrease in muscle performance due to pre-sarcopenia or even sarcopenia factors, which, due to the difficulty of a more invasive methodology in this type of people, its evaluation is greatly limited Koca, I et al., (2015). Likewise, it can be explained even, by an alteration in the kinetics on muscular VO2, Shang, Y et al., (2012), which further aggravates the generalized fatigue, since there is a low maximum aerobic power added to a poor utilization of the same at peripheral level, which translates into a limited cardiorespiratory and neuromuscular condition.

On the other hand, people diagnosed with fibromyalgia also have elevated oxidative stress levels with a decrease in antioxidants with respect to healthy people, Sarıfakıoğlu, B et al., (2014). Which highlights a greater deterioration of neuromuscular functions, with a worse post-exertion recovery, being in this sense the aerobic and strength physical exercise fundamental to alleviate and modify this situation.

These circumstances result in a significant decrease in physical condition and, consequently, in the ability and personal autonomy of the patient in their daily routine, so it is of utmost importance to provide a response through an intervention work that can, both centrally and peripherally, achieve a significant improvement in the quality of life of these people.

On the other hand, several unlinked investigations on the role of the central nervous system (CNS) and nociceptive alterations, as, almost, the only explanation in the currentsCurrent studies on the diagnosis of fibromyalgia disease have shown that there is a mitochondrial alteration at various levels. These mitochondrial alterations include abnormal changes in their structure, a decrease in the number of mitochondria and an increase in their size in this type of person. Cordero, M. D et al., (2011); Sprott, H et al., (2004); Meeus, M et al., (2013), also, it has been found that people with fibromyalgia have lower values in the expression of PGC-1a and Tfam and AMPK with respect to the

control group, Castro-Marrero, J et al., (2013), which may explain and shed light on the reason for many of the symptoms in people with fibromyalgia.

It is known that one of the causes for AMPK activation in conventional exercise and, more specifically, aerobic exercise, is an increase in the AMP-ATP ratio due to the very demands of the activity in terms of intensity and duration so, when at the cellular level they detect an energy imbalance AMPK is activated in the α catalytic domain by LKB1. In hypoxia it has been shown that it is also a trigger for the activation of this protein by LKB1, although the conditions that are met in conventional exercise are not the same as those that trigger this activation because in hypoxia the AMP-ATP ratio does not increase, but rather decreases. On the other hand, hypoxia also produced reactive oxygen species (ROS), postulating the research that, under hypoxia conditions AMPK activation is produced by oxidative stress and not by the AMP-ATP ratio. Emerling, B. M et al., (2009); Morales-Alamo, D et al., (2012).

In other research Hao, Z et al, (2015), where the role of hypoxia, blood flow deprivation and apoptosis in fracture healing, where hypoxia started shortly after the reduction of blood flow by the fracture itself, they proved that severe hypoxia is a limiting factor for fracture healing, but, on the other hand, they proved the role that hypoxia plays in the activation of AMPK, being this a protein activator, concluding that, hypoxia, ischemia and ROS potentially activate the AMPK signaling pathway, Laderoute, K. R et al, (2006).

Training by ischemic hypoxia is called occlusive, ischemic or Kaatsu training. It is a training technique that originated in Japan in the early 1980s and became popular in the late 1990s. This technique is based on the restriction or occlusion of blood flow during exercise, whether aerobic or strength exercise. This methodology was created in response to an aging Japanese population in order to alleviate falls and musculoskeletal disorders typical of age and thus provide an increase in the autonomy of the elderly population. This type of technique is developed as an alternative method to conventional strength training and aerobic exercise, where a physically limited population has a lower adherence at all levels, mainly due to the intensity and duration required to achieve significant physiological adaptations, so that the technique with occlusion makes sense because of achieving positive changes with a lower load to mobilize and less time to execute. On the other hand, the ischemia method is also very widespread in the field of sports performance, presumably due to the fact that the probability of injury decreases if a technique is used that provides the desired adaptations with a lower mobilization load and a more limited training duration, where several studies have shown its usefulness in terms of physiological improvements. Martín-Hernández, J el al., (2011).

These characteristics and previous research confirm the need to carry out research that continues to deepen the level of expression of mitochondrial proteins and their role in the quality of life and functional autonomy from the perspective of a physical intervention program adapted to the conditions mentioned above to carry out a structured and planned program in people with fibromyalgia.

Bibliographic references

- Latorre-Román, P. Á., Segura-Jiménez, V., Aparicio, V. A., e Campos, M. A. S., GarcíaPinillos, F., Herrador-Colmenero, M., & Delgado-Fernández, M. (2015). Ageing influence in the evolution of strength and muscle mass in women with fibromyalgia: the al-Ándalus project. *Rheumatology international*, 35(7), 1243-1250.
- Bonaterra, G. A., Then, H., Oezel, L., Schwarzbach, H., Ocker, M., Thieme, K., & Kinscherf, R. (2016). Morphological Alterations in Gastrocnemius and Soleus Muscles in Male and Female Mice in a Fibromyalgia Model. *PloS one*,11(3), e0151116.
- Valim, V., Oliveira, L. M., Suda, A. L., Silva, L. E., Faro, M., Neto, T. L. B., & Natour, J. (2002). Peak oxygen uptake and ventilatory anaerobic threshold in fibromyalgia. *The Journal of rheumatology*, 29(2), 353-357.
- Koca, I., Savas, E., Ozturk, Z. A., Boyaci, A., Tutoglu, A., Alkan, S., ... & Kimyon, G. (2015). The evaluation in terms of sarcopenia of patients with fibromyalgia syndrome. *Wiener klinische Wochenschrift*, 1-6.
- Shang, Y., Gurley, K., Symons, B., Long, D., Srikuea, R., Crofford, L. J., & Yu, G. (2012). Noninvasive optical characterization of muscle blood flow, oxygenation, and metabolism in women with fibromyalgia. *Arthritis research & therapy*, 14(6), 1.
- Sarıfakıoğlu, B., Güzelant, A. Y., Güzel, E. Ç., Güzel, S., & Kızıler, A. R. (2014). Effects of 12-week combined exercise therapy on oxidative stress in female fibromyalgia patients. Rheumatology international, 34(10), 1361-1367.
- Cordero, M. D., de Miguel, M., & Moreno-Fernandez, A. M. (2011). Mitochondrial dysfunction in fibromyalgia and its implication in the pathogenesis of disease. Medicina clinica, 136(6), 252-256.
- Sprott, H., Salemi, S., Gay, R. E., Bradley, L. A., Alarcon, G. S., Oh, S. J., ... & Gay, S. (2004). Increased DNA fragmentation and ultrastructural changes in fibromyalgic muscle fibres. *Annals of the rheumatic diseases*, 63(3), 245-251.
- Castro-Marrero, J., Cordero, M. D., Sáez-Francas, N., Jimenez-Gutierrez, C., AguilarMontilla, F. J., Aliste, L., & Alegre-Martin, J. (2013). Could mitochondrial dysfunction be a differentiating marker between chronic fatigue syndrome and fibromyalgia?.

- Emerling, B. M., Weinberg, F., Snyder, C., Burgess, Z., Mutlu, G. M., Viollet, B., ... & Chandel, N. S. (2009). Hypoxic activation of AMPK is dependent on mitochondrial ROS but independent of an increase in AMP/ATP ratio. Free Radical Biology and Medicine, 46(10), 1386-1391.

- Laderoute, K. R., Amin, K., Calaoagan, J. M., Knapp, M., Le, T., Orduna, J., ... & Viollet, B. (2006). 5'-AMP-activated protein kinase (AMPK) is induced by low-oxygen and glucose deprivation conditions found in solid-tumor microenvironments. Molecular and cellular biology, 26(14), 5336-5347.

- Martín-Hernández, J., Marín, P. J., & Herrero, A. J. (2011). Revisión de los procesos de hipertrofia muscular inducida por el entrenamiento de fuerza oclusivo. *Revista Andaluza de Medicina del Deporte*, 4(4).

Protocol

Hypothesis

1- The training program has a positive impact on quality of life and functional autonomy in people with fibromyalgia.

2- The training program is effective and generates little fatigue.

3- The training program has a high adherence in people with fibromyalgia.

4- The hypoxia produced and the relative intensity of the program has a direct impact on the balance of oxidant/antioxidant levels.

5- The levels of TAS, MDA, liver enzymes, biochemical variables and hemogram remain stable without significant alterations.

6- Occlusive training in people with fibromyalgia proves to be an effective and safe therapy as part of the treatment.

Objectives

Main Objective

To improve the quality of life and functional autonomy.

Specific Objectives

1- To achieve results by minimizing the fatigue produced in people with fibromyalgia.

2- To get people accustomed to the adapted program and make it part of their routine.

3- To measure variables in blood/plasma to verify the results obtained for a better understanding of the disease and its impact.

4- To identify those blood/plasma variables most susceptible to occlusive training that will allow a better understanding of fibromyalgia disease.

5- To test the effectiveness and adherence of occlusive training in people with fibromyalgia by means of blood/plasma samples, functional tests and questionnaires.

6- To evaluate occlusive training as a valid physical complementary therapy for people with fibromyalgia.

Methodology

The methodology will be carried out by an experimental design research to test the effect of the independent variable on the dependent variable. In this case, the independent variable will be the pressure exerted by the occlusive cuff on the thigh musculature during the planning of aerobic exercise walking of low intensity and reduced time, and its impact on the dependent variable, which is determined by plasma and blood values, mitochondrial protein expression, standardized questionnaires of the impact of the disease (psychometric), and functional tests of physical condition (distances and times performed), which will be measured before and after the intervention period.

Study population

The study population will be men and women diagnosed with fibromyalgia between 18 and 70 years of age from Seville capital and province. In this way, a more representative sample will be included, since both active and sedentary people will be included. There will also be people who are active at work and people who are engaged in housework.

Sample size.

With a 95% CI and a percentage of 1.8% prevalence of the disease in Andalusia for both sexes, according to data collected from the Ministry of Health and Family in the year 2021 of people affected by fibromyalgia with a precision of ± 3%, the sample size is n=75.

Inclusion and exclusion criteria

Criteria for inclusion in the research

- A patient meets diagnostic criteria for fibromyalgia if the following three conditions are present: (American Rheumatology Association). Wolfe et al., (2010).o o 1) Widespread Pain Index (WPI) ≥ 7 and Symptom Severity Score (SS Score) ≥ 5 or WPI 3-6 and SS ≥ 9.

- Symptoms have been present, at a similar level, during the last three months.

- The patient has no other pathology that could explain the pain.

- Recent negative COVID-19 test.

Exclusion criteria

- Other associated pathologies that may hinder the development of the investigation.

- Mobility limitations.

- Injuries that add to those of the disease itself and hinder mobility.

- No medical evaluation of the diagnosis of the disease.

- Negative results in the inclusion tests.

- Cardiac pathologies.

- Blood pressure higher than 130-90 mmHg.

- No COVID-19 test.

Definition of variables

-Independent variables:

- Cuff pressure to produce occlusion.
- Walking time and intensity.

Dependent variables:

- Psychometric questionnaires of impact of fibromyalgia disease:
- Symptom severity index (Sscore).
- Widespread Pain Index (WPI).
- Fibromyalgia Impact Questionnaire (FIQ).
- Multidimensional Fatigue Inventory (MFI-20).
- Blood/plasma measurements.
- Biochemical values.
- Oxidative stress, total antioxidants and Coenzyme-Q values.
- Standardized physical fitness tests
    - Time up and Go test.
    - 30-second chair stand test (Cycles).
    - 6-minute walk test (distance covered).
    - Lower body dynamometer test (Newtons of force).
    - Hand press test (Newtons of force).

Data collection

Data collection will be based mainly on 3 stages.

Stage 1

Once the screening on inclusion and exclusion sections has been passed and carried out, the following should be done:

1. **Standardized disease questionnaires.**
   - WPI
   - SScore
   - FIQ
   - MFI-20

2. **Blood draw by nursing team at Santa Ángela de la Cruz Viamed Hospital (Seville).**

3. **Standardized physical tests to determine baseline physical condition (collection of field work data on a sheet for this purpose).**
   - Time up and Go test.
   - 30-second chair stand test.
   - 6-minute walk test.
   - Dynamometer test with lower body dynamometer.
   - Hand press test.

Stage 2

In this stage the intervention period of 10 weeks will be carried out 2 days per week with a total of 20 sessions and with a duration per session of 20 minutes of occlusive aerobic training. The data collected will be carried out with a daily record sheet for each of the participants.

Stage 3

Once the intervention period is over, all the tests that were carried out in stage 1 will be retaken.

4. **Standardized disease questionnaires**.

- WPI
- SScore
- FIQ
- MFI-20

5. **Blood draw by nursing team at Santa Ángela de la Cruz Viamed Hospital (Seville).**

6. **Standardized physical tests to determine baseline physical condition (collection of field work data on a sheet for this purpose).**

    - Time up and Go test.
    - 30-second chair stand test.
    - 6-minute walk test.
    - Dynamometer test with lower body dynamometer.
    - Hand press test.

Statistical análisis

Descriptive statistics were calculated for each variable. The normality of the distribution of data was verified by the Shapiro-Wilk test. Variables showing skewed distributions were log-transformed to obtain a normal distribution. Relative changes within each group were assessed using a paired Student's t test. To compare baseline variables the Student's t test, standardized differences (±90% confidence level) and qualitative differences were estimated. To detect between-group differences, multiple 2 x 2 (group x time) mixed-analysis of variance was performed and adjustments for multiple comparisons were made using the Bonferroni method by dividing the significance level of 0.050 by the number of comparisons, additionally standardized differences (±90% CL) and qualitative differences were estimated. The effect size of standardized differences was determined by Cohen's d statistic, and the Hopkins' scale was used to determine the magnitude of the effect size, where 0 to 0.19 = trivial, 0.20 to 0.59 = small, 0.60 to 1.19 = moderate, 1.2 to 1.99 = large, and >2 = very large (Hopkins et al 2009). A practically worthwhile difference was assumed when the difference score was ≥0.2 of the between-subject SD. Qualitative assessment indicates the likelihood for the between-group differences to be substantial, referring to possible differences, to likely, to very likely, and to almost certain differences. The probability of a true difference between groups was qualitatively classified as almost certainly not: <0.5%; very unlikely: 0.5% to 5%; unlikely: 5% to 25%; possible: 25% to 75%; likely: 75% to 95%; very likely: 95% to 99.5%; and almost certain: >99.5%. A substantial effect was defined as >75% (Batterham and Hopkins 2006).

- Hopkins WG, Marshall SW, Batterham AM, Hanin J. Progressive statistics for studies in sports medicine and exercise science. Med Sci Sports Exerc 2009;41:3–12.

- Batterham AM, Hopkins WG. Making meaningful inferences about magnitudes. Int J Sports Physiol Perform 2006;1:50–7.

Functional tests

30-second chair stand test

Objectives: (Test No. 1)

1-To assess the strength of the extensor muscles of the knees and hips, responsible for gait failure and falls in 30 seconds.

2-To evaluate the resistance to loss of lower body strength, which causes early fatigue, in 30 seconds.

3- To evaluate the perceived effort and relative intensity of the patient's effort.

Bibliographic references. Validity and standardization

- Collado-Mateo, D., Adsuar, J. C., Dominguez-Munoz, F. J., Olivares, P. R., & Gusi, N. (2017). Impact of fibromyalgia in the sit-to-stand-to-sit performance compared with healthy controls. PM&R, 9(6), 588-595.

Test measurements (variables).

- Cycles performed will be counted
- Modified Borg Perceived Exertion Scale (1-10)
- Pulse oximeter (saturation and heart rate before and after)

Transfer of the test to the intervention period

This test will indicate whether after the training intervention period the patient has increased resistance to loss of lower body strength, with an increase in the number of cycles (standing and sitting) and a lower relative intensity of perceived exertion.

https://upotv.upo.es/video/58da21db238583e0478b48f3

Time and Go test

Objectives: (Test nº 2)

1- To evaluate agility, coordination and dynamic balance.

Bibliographical references. Validity and standardization

- Collado-Mateo, D., Domínguez-Muñoz, F. J., Adsuar, J. C., Merellano-Navarro, E., Olivares, P. R., & Gusi, N. (2018). Reliability of the timed up and go test in fibromyalgia. Rehabilitation Nursing Journal, 43(1), 35-39.

Test measurements (variables).

- The time it takes to stand up, walk a given distance, and sit down again will be counted.
- Modified Borg Perceived Exertion Scale (1-10)

Transfer of the test to the intervention period

This test will indicate whether coordination, balance and agility have improved after the intervention period due to an improvement in the muscular response of the lower body, having a direct transfer to avoid possible falls and stumbles.

https://www.youtube.com/watch?v=8eRQexJzzUE

6-minute walk test

Objectives: (Test nº 3)

1-To evaluate the resistance to the loss of lower body strength that causes early fatigue.

2- To evaluate the aerobic endurance capacity through its physical and physiological condition.

3- To evaluate the perceived effort and relative intensity of the patient's effort.

4-To indirectly evaluate their Vo2max.

Bibliographic references. Validity and standardization

- Heredia-Jimenez, J., Latorre-Roman, P., Santos-Campos, M., Orantes-Gonzalez, E., & Soto-Hermoso, V. M. (2016). Spatio-temporal gait disorder and gait fatigue index in a six-minute walk test in women with fibromyalgia. Clinical Biomechanics, 33, 1-6.

- Pankoff, B. A., Overend, T. J., Lucy, S. D., & White, K. P. (2000). Reliability of the six-minute walk test in people with fibromyalgia. Arthritis Care & Research, 13(5), 291-295.

- Salvi, D., Poffley, E., Orchard, E., & Tarassenko, L. (2020). The mobile-based 6-minute walk test: usability study and algorithm development and validation. JMIR mHealth and uHealth, 8(1), e13756.

- Wevers, L. E., Kwakkel, G., & van de Port, I. G. (2011). Is outdoor use of the six-minute walk test with a global positioning system in stroke patients' own neighborhoods reproducible and valid? Journal of Rehabilitation Medicine, 43(11), 1027-1031.

- Southard, V., & Gallagher, R. (2013). The 6MWT: will different methods of instruction and measurement affect performance of healthy aging and older adults?. Journal of Geriatric Physical Therapy, 36(2), 68-73.

- Burr, J. F., Bredin, S. S., Faktor, M. D., & Warburton, D. E. (2011). The 6-minute walk test as a predictor of objectively measured aerobic fitness in healthy working-aged adults. The Physician and sports medicine, 39(2), 133-139.

Test measurements (variables)

- The distance covered in 6 minutes will be counted (pedometer)
- Indirect VO2max will be calculated using, distance covered (m), sex, age, weight, resting heart rate.
- Modified Borg Perceived Exertion Scale after completion of the test (1-10)
- Pulse oximeter (saturation and heart rate before and after)

Transfer of the test to the intervention period

This test will indicate whether the aerobic endurance capacity has improved, covering a greater distance in the given time with a lower perceived exertion. On the other hand, it will also tell us if your resistance to loss of strength has improved after training and your final heart rate to indirectly determine your ventilatory threshold before and after the intervention with a transfer in efficiency, energy and motor efficiency having an increase in your indirect vo2max.

https://upotv.upo.es/video/5936500f238583f9658b464a

Modified Shuttle Walk test

Objectives (Test nº 4)

1-To evaluate the cardiorespiratory capacity in a simple incremental test.

2-To estimate your peak oxygen consumption.

3-To evaluate your resistance to loss of strength with incremental demand.

4-To evaluate the perceived effort and relative intensity that the incremental demand implies to the patient.

Bibliographic references. Validity and standardization

- Ratter, J., Radlinger, L., & Lucas, C. (2014). Several submaximal exercise tests are reliable, valid and acceptable in people with chronic pain, fibromyalgia or chronic fatigue: a systematic review. Journal of physiotherapy, 60(3), 144-150.

- Leone, M., Duvergé, S., Kalinova, E., Bui, H. T., & Comtois, A. S. (2017). Comparison of bioenergetics of walking during a multistage incremental shuttle walk test and a 6-min walk test in active older adults. Aging clinical and experimental research, 29(2), 239-246.

- Lima, L. P., Leite, H. R., Matos, M. A. D., Neves, C. D. C., Lage, V. K. D. S., Silva, G. P. D., ... & Mendonça, V. A. (2019). Cardiorespiratory fitness assessment and prediction of peak oxygen consumption by Incremental Shuttle Walking Test in healthy women. Plos one, 14(2), e0211327.

- Bradley, J., Howard, J., Wallace, E., & Elborn, S. (1999). Validity of a modified shuttle test in adult cystic fibrosis. Thorax, 54(5), 437-439.

Test measurements (variables)

- The distance traveled round trip in the circuit will be counted.
- Time to test stop will be counted.
- Modified Borg Perceived Exertion Scale after completion of the test (1-10)
- Pulse oximeter (saturation and heart rate before and after)

Transfer of the test to the intervention period

This test will indicate the aerobic endurance capacity without self-regulation of intensity unlike the 6-minute walk test. The energy demand and oxygen consumption will be higher and after the 10-week training period we expect a greater distance covered, lower perceived exertion and an increase in indirect Vo2peak with multiple regression model providing significant data on energy and motor efficiency and effectiveness at higher intensity.

https://upotv.upo.es/video/5a72df02238583bd408b456a

General considerations of the functional tests to be applied in the investigation

1-All functional tests have been carefully chosen and reviewed to subject people to a controlled demand that yields significant results of their physical condition.

2-All functional tests are standardized and have been used in numerous investigations in healthy populations and clinical populations with a variety of diseases to determine fitness variables.

3-All functional tests meet criteria for objective assessment of the impact of fibromyalgia on the patient's functional autonomy.

4-All functional tests are aimed at obtaining the greatest possible transfer with the 10-week intervention period.

5-All functional tests are aimed at obtaining an understanding of the impact of fibromyalgia disease on their quality of life.

Familiarization

Familiarization will consist of 2 phases:

1- Familiarization with the functional tests to be performed (on the same day as the tests).

1- How they are performed and explanation of each test visually.

2- Consideration before performing the tests and resolving doubts.

2- Familiarization with the occlusive training and material:

1- The resting SBP will be taken to establish the training pressure of each participant.

(measurement carried out by a team of nurses from Santa Ángela de la Cruz Hospital. Viamed)

- The cuff pressure will be reflected by the SBP at rest in the arm measured with a tensiometer, to which 20% will be added to establish the SBP at rest of the lower body.

- 20% will be added to the resting SBP of the lower body to establish the lower body cuff pressure.

DA, B., Abe, T., Sato, Y., & MG, B. (2007). Effects of a single bout of low intensity KAATSU resistance training on markers of bone turnover in young men. International Journal of KAATSU Training Research, 3(2), 21-26. (cuff pressure protocol)

- At no time should the cuff pressure exceed 7 % on the visual pain scale (VAS).

2- Familiarization with the material will be completed when each volunteer is able to put on, establish the previously set pressure on a chair and walk with the material.

3- The volunteer should become familiar with the intensity of the exercise. Borg scale 1-10, will be used at all times to establish the relative intensity of each participant at all times, the intensity being no less than 6 and more than 7 points, so several exercises will be performed with and without material for that purpose.

9-week Intervention Period

20 minutes of work with blood flow restriction walking at a relative intensity of 6-7 points on the modified Borg RPE scale in a 2 x 30 meter corridor, with each participant's round trip delimited. After 10 minutes, a non-active rest of 3 minutes of seated flow restriction will be performed, to be followed by another 10 minutes of walking.

Considerations for the intervention period and COVID-19:

- 1- The intervention period will be carried out 2 days per week (Tuesday and Friday) in the afternoon at the Viamed Santa Angela de la Cruz Hospital (Bellavista, Seville).

- 2- Each participant will have the necessary autonomy to carry out the training.

    - Placement of the material
    - Rest in a chair for 3-5 minutes without occlusion.
    - Before finishing the rest, re-set the pressure established for each participant.

- 3- Each participant will have to perform the training session with a surgical mask and the handling of the material will be with latex gloves that will be discarded after finishing the training session.

- 4- Each training session will be carried out with groups of 4 participants simultaneously.

- 5- Halfway through the intervention period, each participant's resting SBP will be measured again in order to make adjustments to the maguitar pressure.

Measurements for each session/participant (variables)

1- Before the beginning of each session:

- O2 saturation and resting heart rate.
    - Constants to check the safety of the beginning

- Motivation level (1-10) (additional information)
    - To be used as a subjective check of the patient in order to verify the weekly evolution and to anticipate solutions to possible complications of the volunteer (abandonment).

- Quality of sleep (very good, fairly good, fairly bad, very bad). Pittsburg Subjective Sleep Scale (additional information)
    - To be used as a subjective check of the patient with the aim of checking the weekly evolution and to anticipate solutions to possible complications of the volunteer (abandonment).

- Pain level (1-10) Visual Analog Pain Scale (VAS).

2- After each session:

- O2 saturation and heart rate
- Perceived intensity of exertion scale at the end of the modified Borg (1-10).
- Pain level (1-10) Visual Analog Pain Scale (VAS).

Timing of phases and weeks.

Phases:

1- Completion of questionnaire of criteria for inclusion in the research and items necessary to be part of it (to be carried out in the fibromyalgia association itself).

2- Blood sampling (to be carried out at the viamed hospital).

3- Previous evaluation of autonomy, quality of life and impact of the disease by means of questionnaires, tests and functional physical tests standardized for this purpose. It will be carried out at the Pablo de Olavide University facilities (CIRF).

4- Familiarization. It will be carried out at the Universidad Pablo de Olavide (CIRF) facilities.

5- Period of research intervention 9 weeks (18 supervised sessions). It will be carried out at viamed hospital. Pain Unit.

6- Final evaluation. It will be carried out in the facilities of Pablo de Olavide University (CIRF).

Weeks:

Week 1

- Monday: Pre-intervention blood sampling, disease impact questionnaires
- Wednesday: Familiarization 1 and functional tests nº 1,2 and 3
- Friday: Familiarization 2 and functional test nº 4

Week 2

- Monday: Familiarization 2 (material and training)
- Friday: Familiarization 2 (material and training)

Week 3 to week 12 (intervention period)

- Tuesday: Intervention period Intervention
- Friday: Intervention period

Week 13 Final evaluation.

- Monday: Post-intervention blood sampling, disease impact questionnaires
- Wednesday: Familiarization 1 and functional tests 1, 2 and 3.
- Friday: Functional test nº 4

Participants' arms.

Participants were divided into 2 non-randomized groups with a total of 37 participants at baseline and overcoming the different phases of exclusion 13.

- **Intervention group:** This group will perform each of the above research stages and perform the occlusive cuff intervention period. n= 7 participants.

- **Non-intervention group**: This group will perform each of the above research stages and will perform the intervention period without the occlusive cuff. n= 6 participants.