

## Effect of Hyperbaric Therapy on Fibromyalgia Symptoms and Cerebral Blood Flow Abnormality

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Volume 2 Issue 4- 2019

Received Date: 11 Nov 2019

Accepted Date: 30 Nov 2019

Published Date: 09 Dec 2019

### 2. Keywords

Fibromyalgia; SPECT-TC; HMPAO; Cerebral blood flow; Hyperbaric oxygen therapy

### 1. Abstract

**1.1. Aim:** to evaluate the effect of Hyperbaric Oxygen Therapy (HBOT) on clinical status and cerebral perfusion in patients with fibromyalgia.

**1.2. Methods:** 57 patients with diagnosis of FMS were treated with 6-weeks HBOT. For each patients we evaluated algometric total scores (ATS) on TPs, intensity of pain by Visual Analog Scale for pain (P-VAS) and quality of life by Visual Analog Scale for quality of Life (QoL) at baseline, after 18 treatments and at the end of therapy. Brain SPECT with HMPAO was performed at baseline and even after 6-8 weeks after the end of HBOT. Volumetric regions of interest (VOIs) have been placed on the images.

**1.3. Results:** We found a statistically significant difference both ATS, P-VAS and QoL between baseline evaluation and after 18 treatments ( $p < 0,01$ ), baseline and end of therapy evaluation ( $p < 0,01$ ) and after 18 treatments and end of therapy evaluation ( $p < 0,01$ ). Images analysis showed that there is a statistically significant difference between mean normalized counts in frontal brain regions, both in right hemisphere ( $0,056 \pm 0,010$  vs  $0,065 \pm 0,010$   $p < 0,05$ ) and left hemisphere ( $0,054 \pm 0,010$  vs  $0,063 \pm 0,011$   $p < 0,05$ ).

**1.4. Conclusions:** We observed a correlation between changes in the brain perfusion according to SPECT imaging and changes in the syndrome severity in patients treated by HBOT. Remission of symptoms seems to be correlated with an improvement of cerebral flow.

### 3. Introduction

#### 3.1. Background

Fibromyalgia syndrome (FMS) is considered one of the most common causes of musculoskeletal pain and disability. It is a chronic painful condition present in 2-4% of the population in Italy, with predominance in females. (6.9% in women and 0.3% in men) [1]. FMS shows a bimodal pattern of incidence: a first peak between 25 and 35 years and a second between 45 and 55 years [1, 2]. This syndrome is characterized by widespread chronic pain, tenderness in the muscles and deep tissues, and fatigue accompanied by other non specific symptoms, including sleep disturbances. In particular, the widespread pain of FMS is a disabling condition and can become quite marked when evoked

by digital pressure at tender points (TPs). Research suggests that pain in FM syndrome may be related to a global dysfunction of cerebral pain processing, notably involving central sensitization.

Aim of this study is to evaluate the effect of Hyperbaric Oxygen Therapy (HBOT) on patient's clinical status and cerebral perfusion.

#### 3.2. Pathogenesis and Diagnosis of Fibromyalgia Syndrome

The pathogenesis of FMS remains largely unknown. Several hypotheses have been advanced, which have led to the definition of FMS as a neuroimmune-endocrine disorder, whereby the molecular mechanisms of neurotransmitter dysfunction are associated with more obvious neurological deficits. Trigger conditions such

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Citation: Lelli L, Effect of Hyperbaric Therapy on Fibromyalgia Symptoms and Cerebral Blood Flow Abnormality. Journal of Clinical and Medical Images. 2019; V2(4): 1-5.

as strong psycho-physical stress or febrile illness (often of viral origin) have been suggested [3,4].

Diagnosis of FMS is very difficult, since it is based only on clinical symptoms and no laboratory investigation is available to confirm the clinical diagnosis of FMS. In 1990 the American College of Rheumatology (ACR) published the diagnostic research criteria for fibromyalgia. The criteria included a history of chronic and widespread pain and the presence of 11 or more out of 18 tender points. Pain was considered chronic and widespread when all of the following features were present: pain in the left side of the body; pain in the right side of the body; pain above the waist; pain below the waist. In addition, axial skeletal pain must be present and the duration of pain must be more than 3 months. A tender point was considered positive when pain can be elicited by pressures of 4 kg/cm<sup>2</sup> or less [5, 6]; In 2010 and later in 2011 ACR criteria were modified: in this new version tender point test is being replaced by a widespread pain index and a symptom severity (SS), but also the case definition of FMS is changed to an illness characterized by self-reported, multiple painful regions and additional key symptoms, such as fatigue, sleep disturbance, cognitive problems and the reporting of extent of somatic symptom. [7-10].

For this reason some scales have been introduced into clinical practice to identify pain intensity and influence of disease on quality of life, like visual analog scales (VAS) [11, 12] and Fibromyalgia Impact Questionnaire (FIQ)[13,14]. These are a standardized and self-administered instruments designed to measure the severity of fibromyalgia disease symptoms with questions regarding pain, health state and limitations on activities of daily living.

Recently studies showed that patients with FMS exhibit significant brain single photon emission tomography (SPECT) perfusion abnormalities [2,3].

### 3.3 Therapy of Fibromyalgia Syndrome

Treatments for fibromyalgia syndrome include both medications and self-care. The emphasis is on minimizing symptoms and improving general health. No treatment works for all symptoms, although medications can help to reduce pain. At present, treatment of FMS favors the use of centrally acting anti-epileptics and antidepressants. Anti-epileptics such as gabapentin and pregabalin (PGB) have been used in FMS with especially encouraging results: 30% reduction in pain intensity in about half of patients and 50% in about one-third. Further, PGB was effective in persistent pain refractory to common analgesics. Antidepressants, by improving the quality-quantity of sleep, can decrease some associated symptoms such as fatigue and gastrointestinal disorders, thereby contributing to the optimization of analgesia in patients with FMS. The antidepressants include tricyclic medications, like

amitriptyline and other selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (SNRIs) including duloxetine and milnacipran. Among antidepressants, inhibitors of norepinephrine were more efficacious than serotonin reuptake inhibitors. Optimal results were achieved by integrating treatments to take advantage of potential drug synergism while assuring a better safety profile, owing to the use of each drug at its lowest effective dose [15-17].

### 3.4 Hyperbaric Oxygen Therapy (HBOT) in Fibromyalgia Syndrome

HBOT is a specialized oxygen treatment that enhances the body's natural healing processes. It consists in exposing the patient to a combination of increased atmospheric pressure and increased level of oxygen in a total body chamber. Many illnesses and injuries fail to heal because sufficient oxygen is unable to reach the damaged area because inflammation, swelling, and reduced blood flow prevent oxygen from reaching injured tissues. Hyperbaric oxygen stimulates blood flow, which allows the growth of new blood vessels into the injured tissue. HBOT provides extra oxygen to tissues and cells with minimal side effects [18].

Recently studies also demonstrated that hyperbaric oxygen therapy (HBOT) shows promising effects in management of chronic pain disorders. These studies demonstrate that HBOT reduce production of inflammation mediators and stimulates nitric oxide (NO) synthesis and NO-dependent release of endogenous opioids as mechanism of antinociception.

HBOT can also induce neuroplasticity and acts on the mitochondrial mechanisms resulting in functional brain changes. [19].

## 4. Materials and Methods

This is a retrospective observational study, including patients with a diagnosis of FMS according to the ACR criteria and treated with hyperbaric oxygen therapy (HBOT) at Misericordia Hospital of Grosseto.

### 4.1. Patients and Clinical Evaluation

We recruited 57 patients (56 women; mean age  $55,8 \pm 9,7$  years, range 33–77 years) (Table 1) with diagnosis of FMS based, in agreement with ACR 1990 and 2010 Guidelines, on the presence of multiple myofascial tender points unbound to significant abnormalities in simple blood tests (full blood count, erythrocyte sedimentation rate, c-reactive protein, creatine-kinase, and thyroid stimulating hormone(TSH)). All patients suffered from chronic widespread musculoskeletal pain, chronic fatigue, morning stiffness, sleep problems, headaches and constipation. They were treated with benzodiazepines, tramadol and pregaba-

lin, without significant beneficial effects on pain and quality of life.

For each patients we evaluated algometric total scores (ATS) on TPs, intensity of pain by Visual Analog Scale for pain (P-VAS) and quality of life by Visual Analog Scale for quality of Life (QoL).

**Table 1:** Patient's characteristics.

Number of patients	Age	Gender (F/M)	Age of diagnosis	Time between symptoms and diagnosis
57	55.8 ± 9.7	56/1	48.7 ± 9.5	11.7 ± 10.7

#### 4.2. HBOT Protocol

All patients were treated with 6-weeks HBOT (36 treatments, normal air at 2.5 ATA) and the average duration of each treatments was 90 min.

#### 4.3. SPECT Imaging and Images Analysis

Recently studies showed that patients with FMS exhibit significant brain single photon emission tomography (SPECT) perfusion abnormalities [20-22], for this reason 20 of the recruited patients underwent to a Baseline Brain SPECT with HMPAO to evaluate brain perfusion. 10 of them had an alterate baseline SPECT. In this group of patients SPECT imaging was performed even after 6-8 weeks after the end of HBOT.

Patients received an injection of 740 MBq of <sup>99m</sup>Tc-HMPAO (99mTc-hexamethylpropylene amine oxime) and were kept at rest for 50 minutes, in quiet surroundings, with their eyes closed, in order to prevent interfering disturbance. SPECT was performed using a double-head rotating  $\gamma$ -camera (General Electric InfiniaHawKeye) equipped with a fanbeam collimator. Data were collected in 64 projections (30s spread) through 360°. Tomographic 3-dimensional reconstructions were performed using a filtered backprojection algorithm and Chang attenuation correction was performed.

Volumetric regions of interest (VOIs) have been placed on the images obtained through the SPECT protocol by an expert nuclear medicine physician; in particular VOIs have been positioned on frontal, parietal, medial-temporal, lateral-temporal cortex, posterior cingulate and cerebellum. For each VOI we collect total counts that were normalized for total counts measured on brain reconstruction in its entirety.

#### 4.4. Statistical Analysis

We performed a comparison between clinical results evaluated at baseline, after 18 treatments and at the end of therapy and the results obtained on the individual brain areas in baseline SPECT and in after HBOT SPECT. A t-test for paired data was performed to verify the existence of statistically significant differences (p-value results < 0.05 were considered statistically significant).

## 5. Results

### 5.1. Clinical Results

At baseline, patients showed the following characteristics: mean number of algometric total scores (ATS) on TPs equal to 132,8 ± 32 and mean value of intensity of pain on the VAS (P-VAS) was equal to 7,6 ± 1,7. Total VAS score for quality of life (QoL) was 51,7 ± 14,6. In addition to the pharmacological therapy patients were treated with 6-weeks HBOT (36 treatments, normal air at 2.5 ATA). We have evaluated the changes in the algometric total score, intensity of pain and VAS values for quality of life after 18 treatments and at the end of HBOT therapy. After 18 Treatments ATS 100,6 ± 33,7, P-VAS 5,8 ± 2,2, QoL the end of therapy 37,6 ± 19,2; after 36 Treatments ATS 69,8 ± 33,8, P-VAS 4,4 ± 2,0 and QoL 17,5 ± 18,6. (Table 2) (Figure 1).

We found a statistically significant difference both ATS, P-VAS and QoL between baseline evaluation and after 18 treatments (p < 0,01), baseline and end of therapy evaluation (p < 0,01) and after 18 treatments and end of therapy evaluation (p < 0.01).

### 5.2. SPECT Images Analysis Results

Visual analysis of baseline brain SPECT demonstrated in 10 patients a diffused cerebral hypoperfusion, in particular in the frontal and the parietal lobes. After HBOT-SPECT demonstrated in the same patients an improved cerebral perfusion with an increase in cerebral blood flow in the frontal areas with respect to the basal study; (Figure 2)

Statistical analysis of the images showed that there is no statistically significant difference between the values measured in the parietal and temporal mesial cortex, posterior cingulate and cerebellum before and after therapy (p > 0,05) (Figure 3).

Instead the analysis showed that there is a statistically significant difference between mean normalized counts in frontal brain regions, both in right hemisphere (0,056 ± 0,010 vs 0,065 ± 0,010 p < 0,05) and left hemisphere (0,054 ± 0,010 vs 0,063 ± 0,011 p < 0,05) (Figure 4).

In left temporal cortex we didn't reach a statistically significant difference too (p = 0,06 in right hemisphere and p = 0,07 in left, but we hope that new studies with an increased number of patients could show promising results (Figure 4).

**Table 2:** ATS, P-VAS and QoL at baseline, after 18 cycles and at the end of HBOT.

Evaluation Time	ATS	P-VAS	QoL
Baseline	132.8 ± 32.0	7.6 ± 1.7	51.7 ± 14.6
After 18 HBOT	100.6 ± 33.7	5.8 ± 2.2	37.6 ± 19.2
End of therapy	69.8 ± 33.8	4.4 ± 2.0	17.5 ± 18.6

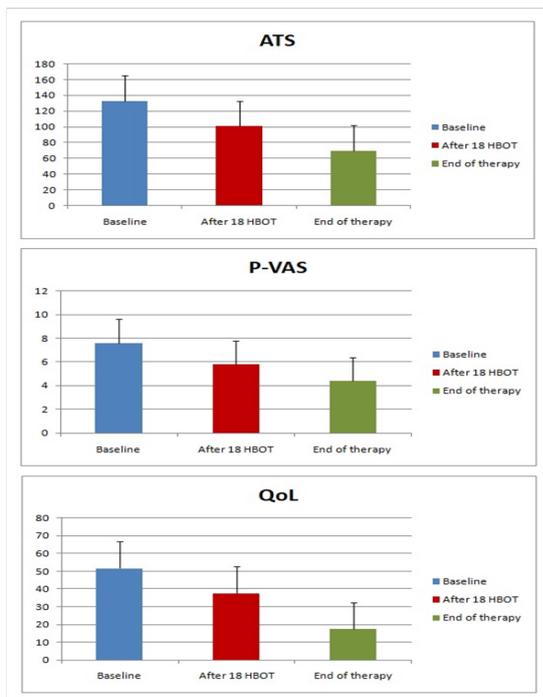


Figure 1: Values in ATS, P-VAS and QoL at baseline, after 18 cycles and at the end of HBOT.

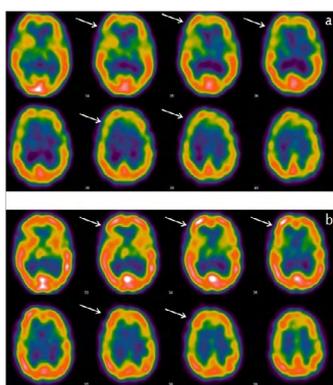


Figure 2: Example of Visual analysis of SPECT images. Significant improvement in cerebral perfusion between baseline SPECT (a) and end of therapy SPECT (b).

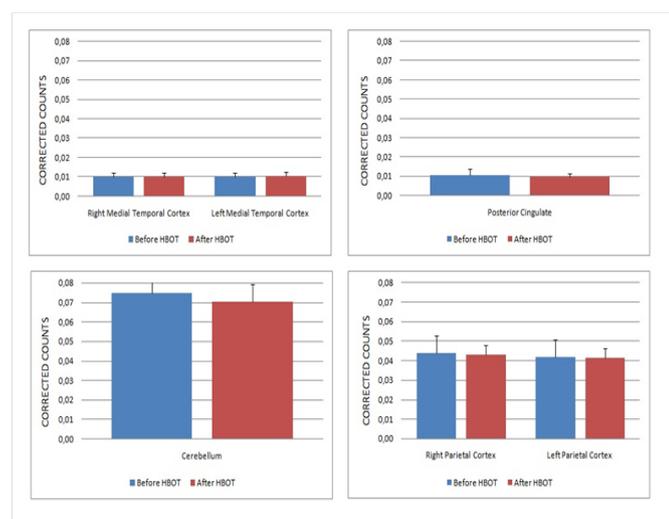


Figure 3: Results on Medial Temporal Cortex, Posterior cingulate, Cerebellum and Parietal cortex.

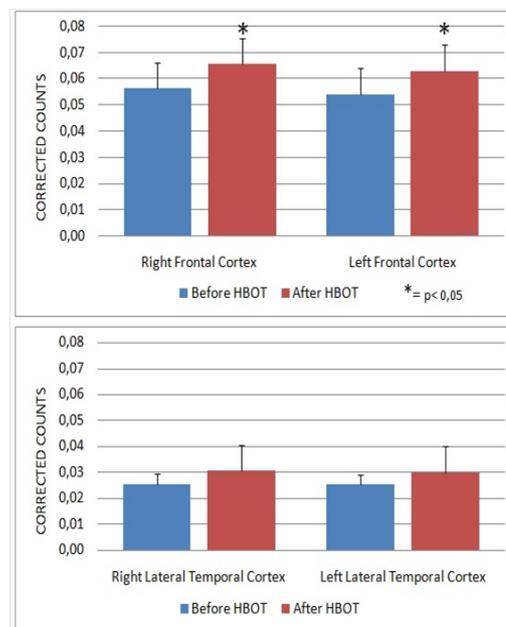


Figure 4: Results on Frontal Cortex and Lateral temporal cortex.

### 6. Discussion and Conclusions

One of the most noteworthy clinical features of FMS is widespread pain that, at particular points called TPs, can reach very high levels when provoked by pressure. Centrally acting anti-epileptics and antidepressants have proven beneficial in reducing pain intensity in patients with FMS, although their effects leave much to be desired. HBOT is highly efficacious in the treatment of chronic pain associated with different diseases and has no deleterious side effects.

We observed a correlation between changes in the brain perfusion according to SPECT imaging and changes in the syndrome severity. Remission of symptoms seems to be correlated with an improvement of cerebral flow. All the patients referred a significant amelioration of all FMS symptoms, and significant improvement in life quality.

The change in cerebral blood flow in specific areas in FMS patients could be related to a dysfunction of pain processing in brain structures, in particular involving central sensitization.

Further studies are necessary to confirm this hypothesis.

### 7. Compliance with Ethical Standards

All procedures performed in the present study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The institutional reviewboard approved this study and all subjects signed a written informed consent related to the imaging procedure, as part of our routine clinical care.

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