A Novel Therapeutic Option for Chronic Fatigue Syndrome and Fibromyalgia

E. BORRELLI, V. BOCCI*

*Department of Surgery and Biomedical Engineering and *Department of Physiology, University of Siena; Italy*

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SUMMARY - The aetiology of chronic fatigue syndrome (CFS) and fibromyalgia remains obscure with a hypothetical primary infection followed by immunological, hormonal and psychological dysregulations. Owing to a failure of orthodox therapies, attention has recently focused on both mental and physical factors although it seems certain that these diseases are not simply due to a psychological condition. Today fairly accepted approaches are based on graded exercise therapy and cognitive behavioural therapy, but they are not always beneficial.

Several biological activities triggered by oxygen-ozone therapy performed with the method of ozonated autohaemotherapy (O_3-AHT) appear suitable to correct muscle hypoxia, immune dysregulation and chronic oxidative stress. Moreover, the induction of a feeling of wellness may effectively contrast the severe fatigue of most patients. However, orthodox medicine has neglected this approach. One good reason is the lack of medical data and this has compelled us to report our very encouraging results in three CFS patients and in five patients with fibromyalgia. One important observation is that therapy must not to be fixed to a rigid cycle but must be continued for several months depending upon the stage and the responsiveness of the patient.

Nuova opzione terapeutica nel trattamento della sindrome da fatica cronica e fibromialgia

RIASSUNTO - *La sindrome da fatica cronica (CFS) e la fibromialgia rappresentano delle patologie ad eziologia non ancora definita causate probabilmente da una ipotetica infezione primaria seguita da una alterazione dei sistemi immunologico ed ormonale e da alterazioni psicologiche. A causa dell'insuccesso delle terapie tradizionali, è stata recentemente posta l'attenzione sui fattori fisici e mentali anche se oramai sembra accertato che la patologia non è causata solo da condizioni psicologiche. Attualmente sembrano metodi terapeutici accettati la terapia basata sull'esercizio graduale e la terapia cognitivo-comportamentale, ma tali misure non risultano sempre di reale beneficio.*

Le molteplici attivazioni biologiche innescate dalla Ossigeno-Ozonoterapia eseguita con il metodo della autoemoterapia ozonizzata (O_3-AHT) sembrano idonee per correggere l'ipossia muscolare, l'alterazione immunologica e lo stress ossidativo cronico presente in tali affezioni. Inoltre, l'induzione del senso di benessere può effettivamente combattere il grave affaticamento di molti pazienti. Tuttavia la medicina ufficiale rifiuta tale approccio metodologico. Una buona ragione è la mancanza di dati medici e tale problema ci ha spinto a riportare i nostri risultati molto incoraggianti in tre pazienti con CFS ed in cinque pazienti con fibromialgia. Una importante osservazione è che tale terapia non deve essere rigidamente eseguita con uno schema prefissato di cicli, ma deve essere continuata per molti mesi a seconda dello stadio e della risposta del paziente.

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Introduction

Chronic fatigue syndrome (CFS) and fibromyalgia are frustrating illnesses characterized by a number of signs and symptoms among which predominate severe fatigue and a flu-like syndrome that profoundly disable patients. CFS has also been named chronic mononucleosis syndrome, chronic Epstein-Barr virus (EBV) syndrome, myalgic encephalitis and postviral syndrome suggesting that the initial cause of the disease was believed to be a viral infection [1,2]. In spite of the fact that more than 4.000 papers have been published on CFS [3], its aetiology and pathophysiology remain ambiguous, but it cannot be excluded that CFS is first triggered by an undefined viral or bacterial infection able to induce a chronic infection with a concomitant immunological dysregulation [4-8]. Interestingly, De Meirleir et Al [9] confirmed Suhadolnik et Al [10] 's finding of an increased level of 2-5 A synthetase in lymphocytes of patients with CFS. This enzyme is an excellent biomarker of an underlying interferon (IFN) synthesis and IFN represents the prototypic cytokine causing a flu-like syndrome [11,12].

However, we cannot say whether a primary infection is also responsible for the disturbance of the hypothalamic-pituitary-adrenal axis (HPA) characterized by low circulating cortisol, dysregulated secretion of central neurotransmitters (serotonin, opioids, arginine vasopressin) and growth hormone [13]. Although the latter disturbance is controversial [14,15], it must be kept in mind because growth hormone regulates the hepatic synthesis and release of somatomedin C, which is a mediator of muscle homeostasis possibly implicated in muscle pain. This aspect can be connected to the muscular alterations detected in patients with CFS16, characterized by mitochondrial dysfunction and oxidative damage documented by an increased level of 8-hydroxy-2-deoxyguanosine in nuclear DNA and malonyldialdehyde in supernatants of muscle homogenates.

Relevant collateral findings have been an impaired oxygen delivery to muscle and a lower rate of creatinine phosphate resynthesis following high-intensity exercise in CFS patients compared to normal subjects [17].

Fibromyalgia is another obscure syndrome that overlaps with CFS. In Italy, it is considered a disease causing considerable socio-economic problems, since it affects about six million people, predominantly women between the ages of 25 to 60 years. The disorder is characterized by musculoskeletal pain, stiffness, easy fatigability, exhaustion and frequent association with headache, unrefreshing sleep, irritable bowel syndrome and dysmenorrhea. Moldofsky et Al [18] demonstrated that a disturbance of stage 4 non REM sleep characterized by alpha-wave intrusion into the delta rhythm may play a role in the development of fibromyalgia.

The pulsatile secretion of growth hormone closely related to stage 4 sleep may therefore become impaired with consequent decreased release of somatomedin C and muscular damage [16].

It is not surprising that the following orthodox treatments have been tested: antivirals (acyclovir, IFN alpha, immunoglobulin G), antidepressants (fluoxetine, amitryptiline, hypericum extract), anti-inflammatory drugs (a variety of cyclo-oxygenase 1 inhibitors, corticosteroids) and metabolic drugs (vitamin B12, magnesium pidolate, Q10 coenzyme, carnitine, nicotinamide adenine dinucleotide). They have proved to be scarcely effective and some of them exert adverse effects [19]. Prolonged rest similar to the deconditioning process occurring during ageing [20] is ineffective or harmful. On the contrary, graded exercise therapy (GET) [21,22] and cognitive behavioural therapy (CBT) [23-25] administered by specialized therapists appears to be an effective intervention for CFS patients.

A working group set up in 1998 to review the management of CFS published a report in 2001 (Report of the Working Party, 2001) [26] and has reached a fairly large consensus on the beneficial effects of GET and CBT. However, Clark et Al [27] pointed out that "none of the rehabilitation approaches is intended to be curative, no approach has been found to be beneficial for everyone, and all can be tainted by poor practice by therapists lacking proper understanding of the disorder". Moreover, the report endorsed an additional approach known as "pacing" which consists in balancing activity and rest.

This state of uncertainty does not help patients and compels us to propose a complementary treatment that has been quietly performed in the last few years yielding a major, often definitive, improvement in most CFS patients. The treatment is based on briefly treating the patient's blood with oxygen-ozone followed by reinfusion in the donor. Unfortunately, orthodox medicine is strongly biased towards Oxygen-Ozone Therapy despite the fact that unjustified bias is the antithesis of science. We are well aware of this and we doubt that it will ever be contemplated in spite of having a precise rationale. Indeed ozonated autohaemotherapy (O_3-AHT):

a) improves blood circulation and oxygen delivery to ischaemic tissues,

b) corrects the dysimmunity due to a possible primary infection,

c) corrects the endogenous chronic oxidative stress by upregulating the antioxidant system and

d) induces, without side effects, a state of wellness and euphoria consequent to the precisely calculated oxidative stress on blood (ex vivo) that acts as a "therapeutic shock".

A decade long period of biological and clinical studies (reviewed in Bocci [28,29]) completely overlooked by official medicine, support the validity of properly performed Ozone Therapy.

Patients and Methods

Owing to the limitation of recruiting patients this is an open, preliminary trial where patients are compared to those without treatment. The diagnosis of CFS was made on the basis of the definition of the disease made by the US Centers for Disease Control and Prevention [30]. This includes the manifestation of several physical symptoms such as severe fatigue during the last six months and at least four of the following symptoms: 1) sore throat, fever, muscle pain, multi-joint pain, frequent headaches, unrefreshing sleep, impaired memory and post-exertional malaise. The British criteria [31], that insist on the presence of mental fatigue, was also taken into consideration.

The study population consisted of three patients with CFS (one man: age 47 and two women: age 51 and 55) and five patients (one man and four women: mean age 51.5 ± 2.3 years) with fibromyalgia. In this case, the diagnosis was made if at least 11 of the 18 tender points designated by the American College of Rheumatology, elicit pain when pressed. These patients reported easy fatigability, muscle weakness, sleep disturbance and two had frequent headaches.

Pressure over tender sites very often elicited considerable but transitory pain. All of these patients had suspended medical treatments for at least three months. A few patients with depressive disorders taking antidepressants and other drugs were excluded. Before Ozone Therapy, patients were informed that the treatment was experimental but it had a rational basis and did not yield toxic effects. All patients signed a specific informed consent form.

The therapy consisted of O_3-AHT twice weekly (monday and thursday or tuesday and friday). The O_3-AHT treatment in several pathologies has been repeatedly approved by the Ethical Committee of the University of Siena.

This was performed with an atoxic, optimized procedure using glass flasks under vacuum (no plastic autotransfusion bag!) as described in the appendix [29]. We have been very cautious and withdraw only 100 ml of blood (either with a G 19 or 21 needle) supplemented with 11 ml of Na Citrate 3.8%. 100 ml of gas (O_2-O_3) was added (1:1 ratio) first with an ozone concentration of 20 µg/ml rising to 40 µg/ml after two weeks. Ozone concentration was precisely checked by photometry. Thus, the final maximal ozone dose was of 4 mg. After 10 min of gentle mixing, the ozonated blood was reinfused into the donor in about 10 min. The three CFS patients received 28, 32 and 40 initial treatments (during 3.5, 4 and 5 months, respectively) followed by three months'rest. After this period, we suggested resuming therapy if necessary.

Four of the five fibromyalgia patients received between 24 and 36 treatments depending upon the response to Ozone Therapy. As Loconte previously reported [32] we performed careful infiltration of 5 ml of gas (O_3 concentrations: 5-15 µg/ml) in some of the tender sites and trigger points, alternatively. All patients throughout the therapy were advised to supplement their daily diet with vitamin C (0.5 mg), n-acetyl-cysteine (0.6 mg) and a multivitamin tablet (RD doses) including vitamin E, selenium and alpha-lipoic acid.

Biochemical determinations: before starting the therapy, we tested the total antioxidant capacity (TAS) of the patient's plasma. Levels ranged within normal levels (1.3-1.8 mM). Occasionally we tested the TAS level after ozonation and we found that it was decreased by no more than 10%. Peroxidation levels (TBARS) barely increased with an ozone concentration of 20 µg/ml but they were significantly increased after 40 µg/ml to indicate an effective reaction. As a further proof, a 20-30% of protein thiol groups were oxidized. Haemolysis always remained at negligible (0.1-0.4%) levels. These tests described elsewhere [29] make sure that ozone has indeed reacted with blood.

Results

The weakness of our work is due to the very limited number of patients. However, the compliance was excellent and only one dropped out during treatment: as the patients slowly found benefit, they were enthusiastic to continue the therapy. Of the three CFS patients, most of the symptoms decreased after 3.5 and 3 months, respectively of continuous therapy. All of them were and felt practically normal six months after the initial treatment. No side effects were reported and all of them experienced a feeling of renewed energy and euphoria.

Of the five fibromyalgic patients, four showed a definitive improvement after six months whereas one woman had very poor venous access and complained of blood extravasation. After four treatments she was dissatisfied and dropped out. We suggested trying rectal insufflation of O_2-O_3 but she did not accept. The problem of difficult venous puncture is rare but is real and now we can propose the option of quasi-total body exposure to O_2-O_3 that is not invasive and quite practical [34]. During the therapeutic session we take care to talk to the patient and explain the various biological effects resulting from the interaction of blood with ozone. Most of the patients appreciate the conversation and we believe that this is part of the treatment. What its relative role is in comparison to Ozone Therapy remains to be clarified.

Finally, the infiltration of O_2-O_3 in both tender and trigger points of fibromyalgic muscles deserves a comment. Although they cause a transitory (3-5 minutes) pain, they usually elicit a diffuse analgesic effect after 5-8 infiltrations repeated every week.

Discussion

Standardized medical care (antidepressants, glucocorticoids, immunotherapy and metabolic drugs) is scarcely beneficial and with some side effects in CFS patients. Although GET [21,22] and CBT [23-25] appear to represent an effective intervention, they do not entirely solve the problem of two similar syndromes that are likely due to a number of pathogenetic factors. During the last seven years of clinical experimentation in vasculopathic and in age-related macular degeneration patients [29], we consistently noted that O_3-AHT often yields a feeling of well being and euphoria. This result is interesting and we can only speculate that the reasons for these positive effects are due to a functional restoration of hormonal and neurotransmitter functions. Why not then try the "therapeutic shock" of O_3-AHT in patients plagued by fatigue and depression? Moreover, Ozone Therapy may change the vicious circle due to a chronic oxidative stress and deranged muscle metabolism. The clinical results so far obtained appear to justify the use of ozone in this frustrating pathology. It is worth noting that Ozone Therapy is effective because it is able to activate simultaneously several metabolic pathways that have gone astray. This also explains why CBT [23-25], that certainly involves the psycho-neurohumoral system, is somehow more effective than using single conventional drugs. Obviously, our data need to be expanded and compared with a group of patients treated with CBT. The use of a placebo (single autotransfusion or only oxygenated blood) would be interesting, but these patients are severely distressed and randomisation appears unethical.

A few observations ought to be kept in mind for the future. Our schedule and the volume of blood exposed to O_2-O_3 may not have been optimal because the clinical improvement has progressed slowly. While we are insisting [29] on the validity of the strategy "start low, go slow", we may have been too cautious.

The schedule of two treatments per week appears valid and well accepted by patients but while we should start with a 100 ml volume of blood and an ozone concentration of 20 μg/ml, during a four week period, we should escalate the blood volume to the maximum of 225 ml and an ozone concentration of 40 μg/ml. It also appeared clear that a priori we cannot fix a number of treatments (say 12 or 16 to be performed in 1.5 or 2 months) because, understandably, each patient responds differently to the therapy. In our case, among CFS patients, we noted one slow, one medium and one rapid responder. Consequently, we must adjust the cycle and maintenance therapy to the single patient and not to a fixed, meaningless scheme. This is an aspect that ought to be extended to other pathologies.

In the case of fibromyalgia, our statistics are very meagre compared to those reported by Loconte [32] and Cosentino et Al [33]. The latter group determined a complete response in about 40% of patients while Loconte [32] claimed to achieve total remission in 60% of patients. In our case, four patients had an excellent response and this is most likely due to our far longer treatment schedule. The direct infiltration of tender sites and trigger points can be compared with the "chemical acupuncture" [29] performed in the paravertebral muscles for the problem of backache and is interpreted to activate the anti-nociceptive system via the descending analgesic neuronal complex. It may be interesting to evaluate the local infiltration of a small volume of ozonated blood that may lead to a complete normalisation of nociceptors. As we are opening a Regional Ozone Therapy Center at the University Hospital in a few months, we hope that we will be able to recruit more patients and extend these initial observations.

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Prof. Velio Bocci
Department of Physiology
University of Siena
via A. Moro
53100 Siena
e-mail: fisgen@unisi.it