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Fibromyalgia Treated with an Anti-Inflammatory Amino-Acid-Vitamin Complex- A Double Blind, Placebo-Controlled Study for Management of Pain and Sleep Disorders

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Abstract

Based on the hypothesis that pain in fibromyalgia syndrome (FMS) evolves from oxygen radicals and an inflammation within the propagating pain pathways of the brain, an amino-acid-vitamin complex (AAVC) was used for scavenging excess oxygen radical formation and the taming down of inflammation. 20 patients fulfilling criteria for FMS, were given the AAVC orally bid for 12 weeks, while taking their standard medication. For comparison, 15 patients were given a placebo. Compared to start and to the placebo group, AAVC significantly ($p < 0.05$) increased tolerance to pressure at tender points (algometric tension meter; kg) while reducing intensity of spontaneous static pain using the VAS (1-10). Electrical current thresholds for perception of pain, and the tolerance to electrical pain threshold (mA) increased significantly ($p < 0.05$) only in the verum group. Also, feeling of well-being increased significantly ($p < 0.05$) when compared to placebo. In addition, quality sleep improved, which however was not significant to placebo. Malondialdehyde (MDA) levels in urine, reflecting lipid oxidation of cells and the increased formation of peroxide radicals, dropped in the verum group at a significant level ($p < 0.01$). Among patients in the verum group, 50% could either reduce or totally omit their regular pain medication. Oxygen radicals may play a role in the pathology of FMS reflecting ongoing inflammation and the production of oxygen radicals. Intake of AAVC presents an intriguing new complementary concept in patients with FMS-related pain.

Keywords: *Fibromyalgia; Static-Experimental Pain; Free Radical Formation; Antioxidant Therapy; Amino-Acid Vitamin Complex*

Introduction

Fibromyalgia syndrome (FMS) is an often under-diagnosed disorder of unknown etiology affecting over 5% of patients in general practice and an estimated 2 - 4% of the general population [1]. Patients complain of chronic, diffuse musculoskeletal pain, which is associated with typical widespread tender points at the muscular tendon junction. FMS occurs predominantly in women (10:1) between the ages 20 - 60 years and approximately 75% of all patients present an associated fatigue, non-restorative sleep, and widespread stiffness, while 25% of all patients present an irritable bowel syndrome, a wandering paresthesia at different points of the body and anxiety or depression, associated with a functional disability [2,3].

While the etiology of FMS is surrounded by many theories and is far from being solved, the diagnostic, laboratory tests are only useful as exclusion criteria in the sense that they rule out other pathologic condition [4]. Because of the lack in specific changes in muscle biopsy specimens [5,6], NSAIDs are of little value. In spite of the greater prevalence of depression, anxiety, and somatoform disorders, the majority of patients reveal no active psychiatric disorder. And while the stable pain patterns argues against a hysteric disorder [7,8], the advocated treatment are low dose antidepressants in a dose range, which make it unlikely that the beneficial effect is due to an amelioration of depression [9,10]. Although painful symptoms may be relieved both by pharmacological and non-pharmacological treatment such

as cognitive-behavioral therapy [11], biofeedback [12] and aerobic fitness training [13], the pain syndrome nevertheless persists for years leading to patient perception of disability and total disability payments of up to 9% [14].

In the search for non-pharmacological treatment in FMS, and because of an often insufficient relief from pain and stiffness with the conventional medication, we considered a complimentary approach using an amino-acid-vitamin-complex (AAVC) in patients who experienced insufficient pain relief with their conventional antidepressant, opioid and/or NSAID medication. Treatment of FMS patients with an AAVC was based on the hypothesis that due to a dysfunction in serotonin synthesis [2,15] there is an resulting reduced activity of the descending inhibitory pain system [16]. By administering precursors of serotonin synthesis it was felt that this insufficiency could be reduced. In addition, oxygen radicals and superoxide [17] being involved in the formation of NO, present a contributing factor in the increase of nociceptive processing [18]. Scavenging of oxygen radicals with an AAVC therefore seemed of additional benefit. And because AAVC has no side effects such as the usual prescribed medication, complimentary therapy would result in higher quality of life.

Materials and Methods

Following informed consent and after approval by the local ethical committee, 60 patients with a long-lasting (> 3 years) fibromyalgia syndrome, who demonstrated insufficient relief with their current medication, were screened to enter the study. Of these 60 patients, forty fulfilled all criteria for the classification of fibromyalgia of the American College of Rheumatology [19] and were compliant enough to participate (Figure 1). They were randomly assigned to either the verum or the placebo group (Figure 1). In short, criteria for the classification of fibromyalgia consisted of tender points, which had to be present on both sides of the body, above and below the waist and in the midline with widespread pain for at least three months. Tenderness should be of focal nature rather than diffuse, and tender points had to be positive in 11 of a total of 18 on digital palpation points using an approximate force of 4 kg at typical locations described in detail elsewhere [19]. In addition, patients presented an inability to have a refreshing and restorative sleep and low level of well-being.

Twenty patients (15 female and 5 male) with a mean age 52.5 years (± 5.0 SD), a mean height of 163.3 cm (± 9.0 SD) and mean weigh of 71.5 kg (± 11.0 SD) were given an amino-acid-vitamin-complex (AAVC) preparation twice daily over a period of twelve weeks in a single-blind fashion. The preparation was specifically composed for the study and consisted of the following components and dosages:

1. L-Carnitine (500 mg), a powerful antioxidant, has been shown to be useful in the treatment of chronic fatigue syndrome, often a co-existing ailment in FMS patients. In addition, the agent also activates T-and B-lymphocytes and is a necessary adjunct in the energy supply for muscle activity [20].

2. L-Tryptophan (500 mg), a necessary precursor in serotonin and melatonin synthesis [21], thus reducing pain and affecting quality of sleep [22].

3. L-Histidine (300 mg) has been shown to be a helpful adjunct in patients suffering from rheumatoid arthritis pain [23].

4. L-Phenylalanine (300 mg), has been shown to be helpful in increasing pain-threshold [22].

5. L-Lysine (500 mg), in combination with vitamin C has been shown to be an efficient adjunct for the synthesis of carnitine [24].

6. S-Adenosyl-methionine (300 mg), is a powerful antioxidant, increases pain-tolerance and in addition, is an important precursor in the formation of a major antioxidant glutathione [22].

7. L-Tyrosine (300 mg) is a useful therapeutic adjunct in patients with a low activity index and reduces chronic fatigue disorders, often a co-morbidity in FMS patients [22].

8. Taurine (1000 mg), is a major antioxidant protecting the cellular membranes against toxic oxygen radicals and a necessary fuel for mitochondrial function [25].

9. Vitamin C (300 mg) a co-factor in the formation of serotonin and adrenaline, given together with
10. Vitamin E (30 mg), both of which portray powerful antioxidative activity [26,27].
11. Vitamin B-complex consisting of the important constituents vitamin B6 (5 mg) and vitamin B12 (10 µg), which play a crucial role in nociceptive transmission.
12. Magnesium (100 mg) is a cofactor in the formation of serotonin and melatonin, and a necessary adjunct to reduce pain transmission by means of selective blockade of the excitatory NMDA-receptor [28].
13. Omega-3-fatty acids (EPA 300 mg), which block the formation of the inflammatory cytokines TNFα and IL-1ß [22], which are formed in excess during oxygen-derived free radical stress.

For comparison purposes, a placebo group consisting of twenty patients (5 lost at follow up leaving 13 female and 2 male; table 1) with a mean age of 47.4 years (±9.0 SD), a mean height of 168.3 cm ± 8.2 (SD) and mean weigh of 64.2 kg (±11.0 SD) took a similar looking mixture twice/day for 12 weeks.

In order to demonstrate efficacy of AAVC, the following variables were measured before and 4, 8 and 12 weeks following intake of AAVC:

1. Tolerance to pressure (kg) on typical tender points using a scaled pressure algometer to a point where painful sensations were perceived by the patient.
2. Individual thresholds for perception and tolerance of pain sensations induced by rectangular electrical stimuli of 0.5 ms duration and a frequency of 5 Hz. Electrical current (mA) was increased in an ascending staircase fashion (Digi Stim®II, Neurometrics, Houston, Texas, USA) via two 1 cm diameter Ag/AgCl stick-on electrodes placed on the volar part of the underarm.
3. Quality of sleep using a visual analog scaling between 0 (worst possible sleep) and 10 (relaxing and refreshing sleep) and feeling of well-being, using an analog scaling between 0 (worst possible feeling) and 4 (joyful, content feeling).
4. Intensity of spontaneous static pain, using a visual analogue scaling (VAS) between 0 and 10, where 0 depicts no pain and 10 the worst possible pain.
5. Malondialdehyde (MDA) concentration in the morning urine, a sensitive marker reflecting insufficient antioxidative activity to scavenge toxic oxidative radicals [29]. Since free oxygen radicals result in a higher degree of lipid oxidation of cells and an ensuing formation of MDA, a semiquantitative colorimetric method (Orthomol®Redox, Orthomed company, Langenfeld/ Germany) was used [30-32]. With this test it was possible to quantify the antioxidant reserve and determine possible positive effects following AAVC intake.

Statistical analysis

Before starting the study, a statistical a priori analysis was performed. This was indispensable in order to establish the number of patients necessary to demonstrate a statistical significant difference. Based on the results of a previous study [33] for scavenging toxic peroxide radicals with reduced glutathione (GSH), the intention was to detect an increase of maximal pain threshold values by 50%, an effect level of 1.0, with an a-error of. 0.5. Using ANOVA the study population was calculated to be 10 participants in order to reach a minimum power of 80%. For calculation of statistical differences before and after 12 weeks of treatment the two-way analysis of variance with Bonferroni correction was used. Fischer exact test was used to determine significant difference in urine malondialdehyde concentration. Significance is defined if p is < 0.05.

Results

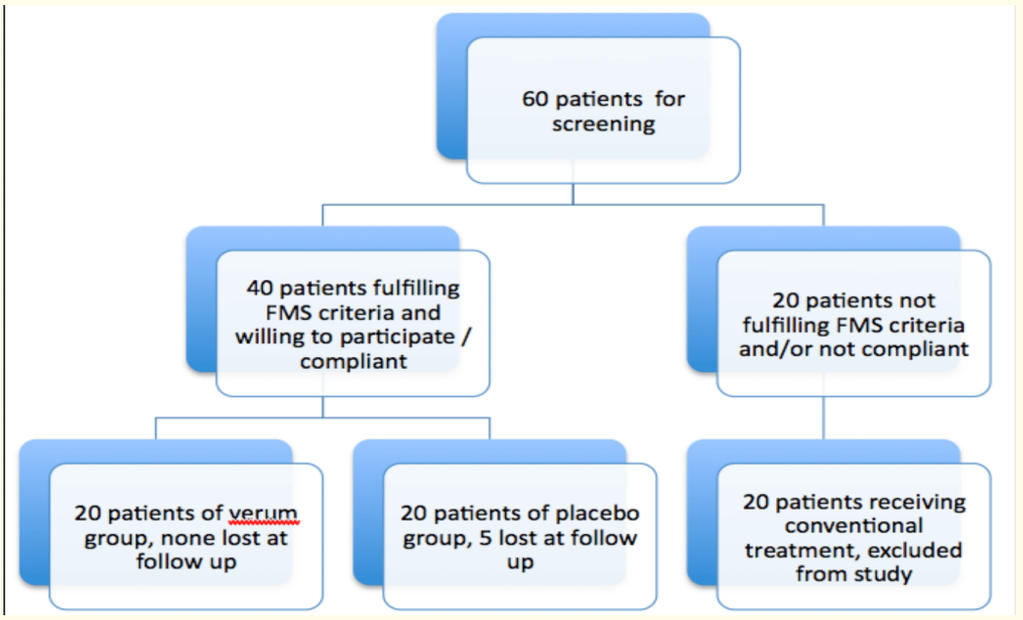
Both groups of patients demonstrated no statistical significant difference in regard to age, height, and the duration of their ailment (Table 1). And although mean weight of the control group was higher than in the verum group, this was statistically not significant. Also,

there was some difference in regard to the type of medication being taken for the relief of the ailment. Patients in the placebo group had a higher incidence in use of a centrally muscle relaxant (i.e. diazepam). This difference, however, was statistically not significant (Table 1).

Groups	Age (years)	Height (cm)	Weight (kg)	Medication Opioid/ Antidepressant/ NSAIDs/ Peripheral Relaxant	Gender Female/Male
Verum n = 20	52.5 ±5	163 ±9	71.5 ±11	5 - 5 - 6 - 4	15/5
Placebo n = 15	47.4 ±9	168 ±8	64.2 ±11	4 - 7 - 7 - 6	13/2

Table 1: *Demographic data of patients participating in the study using an AAV-complex (verum group) or a similar looking non-active formulation (placebo group) for treatment of FMS symptoms (mean +/- SD).*

Compared to the pre-medication period and following 12 weeks of therapy with the AAVC, mean sensitivity threshold level to an applied pressure force on 12 of 18 tested typical tender points increased significantly and compared to placebo ($p < 0.05$). This is demonstrated in figure 1, where the overall 2-fold increase in tolerance to mechanical pressure demonstrates an increase in pain threshold at the muscular-tendon junctions. Such difference in increase of tolerance to pressure at predefined tender points was not seen in the placebo group.



Flow chart: *Flow chart of FMS patients admitted to a treatment with an AAV-complex for 12 weeks.*

In addition to the increase of tolerance to pressure, patients also developed an increase of tolerance to experimentally induced pain. Compared to the control situation at start of the study and compared to the placebo group, only patients of the verum group showed an increase of tolerance. This difference was statistically significant at the $p < 0.05$ level (Figure 2) at three perception levels. Thus, the threshold for sensing the electrical stimulus increased from a mean of 0.45 mA (± 0.2 SD) to a mean of 0.93 mA (± 0.1 SD). This increase is highly significant ($p < 0.005$). In addition, the threshold level for perceiving pain sensations, and the threshold for tolerance to the electrical current increased significantly ($p < 0.05$; Figure 2).

Parallel to objective measurements, subjective rating of static pain intensity (VAS) at the start of the study was 6.0 and 5.7 in the placebo and the verum group, respectively. Following 12 weeks of AAVC subjective pain rating decreased to a mean of 4.1 (± 1.2 SD) in the verum and to a mean of 5.5 (± 1.1 SD) in the placebo group. This change reflects a significant change at the $p< 0.05$ level in favor of the verum group. Also, quality of sleep increased significantly ($p < 0.01$) within the verum group; however, this was statistically not significant when compared tom the placebo groups ($p < 0.336$). This is in contrast to the subjective rating of well-being. When compared to the start of the study, there was a significant increase ($p < 0.05$) within the verum group, and there was also a statistical significant difference ($p < 0.05$) when compared to the placebo group (Figure 3).

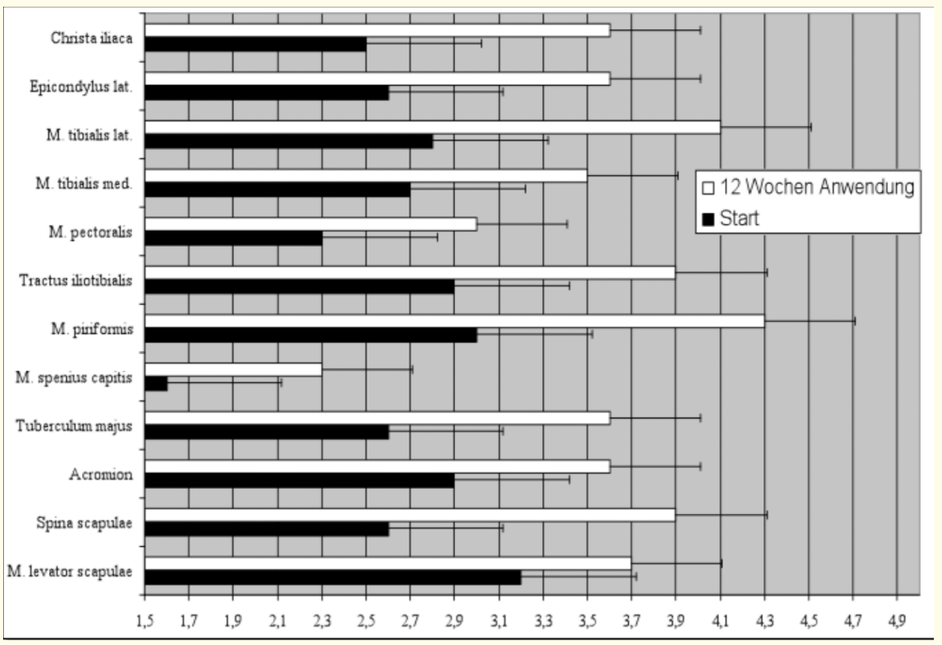


Figure 1: *Increase of tolerance to pressure at different musculo-skeletal junctions (tender points) in patients with FMS using an AAV-complex for 12 weeks (mean +/- SD; black bar= before; open bar= after treatment).*

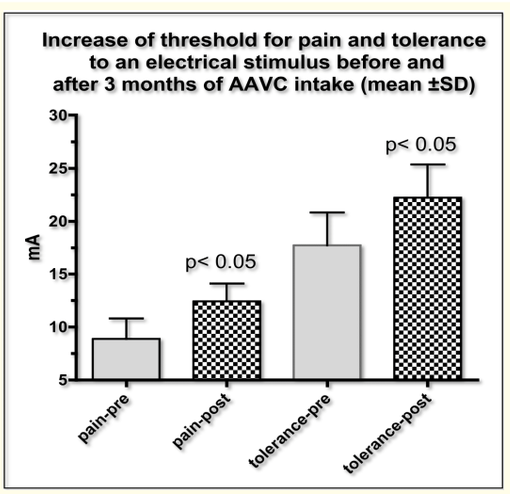


Figure 2: *Changes in artificially induced pain (threshold in mA; rectangular electrical stimulus) in patients with FMS before and after 12 weeks of treatment with an AAV-complex (mean +/- SD).*

Concentrations of the metabolite malondialdehyde (MDA) in urine specimens were tested highly positive in both groups of patients at start of the study. Only in the verum group mean concentration of MDA declined from > 2.0 mmol/l to a mean of < 1.0 mmol/l following 12 weeks of amino acid/vitamin therapy. Such a decline was not found in the placebo-group, reflecting a statistically highly significant difference ($p < 0.01$) between the two groups (Table 2, Figure 4).

Groups	Before (µmol/l)	After (µmol/l)
Verum	2.2 ± 0.8	0.7 ± 0.7**
Placebo	2.5 ± 0.9	2.2 ± 0.9

Table 2: *Malondialdehyde levels (mmol/L) in FMS patients with and without a 12 week intake of an AAV-complex (mean +/-SD; **p < 0.01).*

In order to assess if the reduction in MDA somehow is intertwined with changes in spontaneous pain, and assuming that the scatter of data is not gaussian, polynomial first order, nonlinear regression analysis was done. There was a positive relationship between both parameters with a slope of 0.69, yielding an equation $y = 0.92 + 0.69^{x}$. Thus, patients of the verum group who demonstrated a pronounced decline in MDA levels also displayed a reduction in spontaneous pain VAS scores.

Last but not least, another beneficial effect of the AAVC medication was observed in some patients at termination of the study. Several patients (n = 3) who had been on potent opioid medication such as transdermal fentanyl (Durogesic®) or transdermal buprenorphine (Transtec®) could omit these analgesics. In other patients the dosage of daily NSAIDs could be reduced markedly (n = 6) or totally skipped (n = 1). And finally, one patient stopped the daily intake of a benzodiazepine for relief of muscle spasm and sleep deprivation.

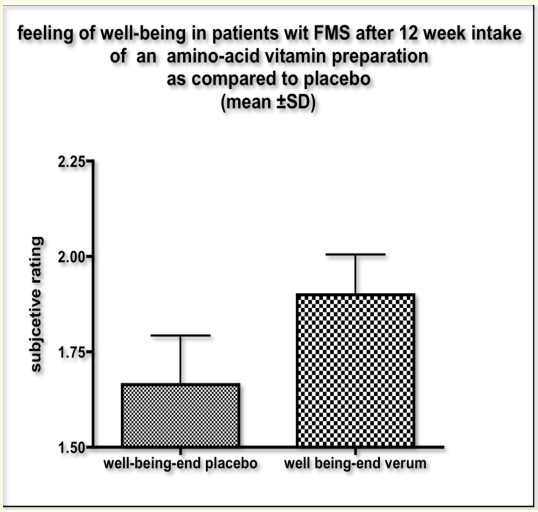


Figure 3: *Well being of patients after intake of an AAV-complex (verum group) compared to placebo in patients with FMS ($p < 0.05$).*

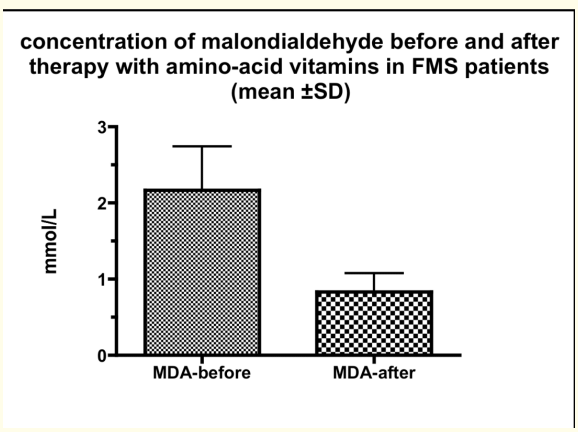


Figure 4: *Decline in MDA in patients following intake of an AAV-complex for 12 weeks ($p < 0.01$).*

Discussion

Although the present results do not answer the intriguing question of the origin of FMS, they do, however, give further insight into the possible mechanism of pain in fibromyalgia patients. The low threshold to pressure at specific tender points in FMS patients typically reflects the increased sensitivity to an otherwise non-nociceptive stimulus. The AAVC was able attenuate such increased sensitivity. While this may mirror a reduction of a highly sensitive peripheral nociceptor system and/or a reduction in the previously increased transduction of painful stimuli, it may also reflect an increase of activity of the descending inhibitory pain system. Reduction in peripheral sensitivity is further supported by the increase of threshold to an electrical stimulus, necessary to perceive a sensation, the threshold on perception of pain, and the level of tolerance to the electrical stimuli. Pain threshold testing, by means of electrical current presents a technique, which has been established in numerous pain studies [34,35]. When used in the present context, patients with FMS demonstrate a low peripheral threshold to a given stimulus, which reflects a decrease in activity of the descending inhibitory system in our patients. Such presumption can be derived from data in a control population where mean threshold value for electrical perception is 10-fold higher (mean 7.5 mA versus 0.71 mA) than in the present FMS patients [36]. Following intake of AAVC, the significant increase of low electrical

current threshold corroborates also the assumption of others, that activation of the descending inhibitory system is the primary mode of action when relieving pain in FMS patients with an antidepressant [21,37]. It therefore seems permissible to speculate that composites of our AAVC (L-tryptophan and L-tyrosine) may present an increase in synthesis of serotonin resulting in an amplification of activity of the descending inhibitory pain pathways with pain relief [38].

In addition to the increase in threshold values to experimental pain, the present results on fibromyalgia patients demonstrates that this pain consists of two entities: One with a lowered threshold for external stimuli resulting in an increase in nociceptive activation with an augmented sensitivity at tender points. Second, a sensitization of stimuli to higher cortical centers, termed as central pain. Such sensitization of nociceptive afferents with an ensuing low threshold level was seen not only in our set of patients. Other researchers, who used laser-evoked somatosensory potentials in the EEG and showed lower heat pain threshold than a control population, confirm the present findings. But more important, these authors demonstrated a broader distribution of evoked potential over cortical areas, which is in contrast to the restricted contralateral and midline position of potentials in control subjects [39].

Taking together our results and the data from sensory-evoked potentials, which demonstrate a broader distribution over cortical areas, hyperalgesia in fibromyalgia patients is compatible with the notion that pain in FMS is both due to an increase of sensory-perceptual and cognitive stages of nociceptive processing [40,41]. It is because of this twofold differentiation, that sensory perception primarily can be influenced by the descending pain inhibitory control system, while centrally mediated cognitive stages of nociception are more robust against conventional therapy. Such assumption is underlined by the present data, where the threshold levels for sensation to a given peripheral electrical stimuli were not significantly affected by complementary AAVC when compared to placebo. In contrast, a significant therapeutic effect was seen on the threshold levels for tolerance to the evoked electrical stimuli, suggesting a distinct and separate endogenous factor, i.e. central sensitization to stimuli in FMS. Central sensitization therefore seems to represent an entity of nociception in fibromyalgia, which needs a different approach in therapy, putting additional attention on cognitive behavioral therapy [11].

Aside from a beneficial effect on spontaneous pain, the AAVC may protect cells from oxidative degradation. This presumption is underlined by the present data, where the formation of malondialdehyde, a marker for breakdown of unsaturated free fatty acids, declined after 12 weeks of therapy. And since there was a close relation in the amount of reduction of free radical induced formation of malondialdehyde and the level in static pain, AAVC can be regarded as a superoxide dismutase (SOD) mimetic, as it restores the imbalance of toxic oxygen radicals and endogenous SOD. The hypothesis of an oxidative stress-related pain in fibromyalgia has been corroborated by another study [33]. There the potent oxygen radical scavenger reduced glutathione (GSH) was able not only to significantly reduce acute pain sensations at tender points in FMS patients. AAVC also attenuated subjective pain ratings and increased the feeling of well-being within two months of treatment. In regard to the endogenous formation of GSH, there are several major components in the present AAVC, which contribute to the formation of GSH. Thus, taurine, S-adenosyl-methionine, carnitine, vitamin C and E all may very well contribute to an increase in the oxidative stress scavenger system underlining the present findings in some patients who, while taking opioids (i.e. tilidine, fentanyl TTS or buprenorphine TDS) or on NSAIDs, could either reduce their daily dose or could totally omit intake. It therefore deems necessary to evaluate such beneficial effect on a larger number of patients and over a longer period of time, especially since formation of reactive oxygen species (ROS) also termed as oxidative stress, is attributed to a number other painful ailments [17,42-44].

There are several limitations in the design of the present study. First and most of all, the control group consisted of a lower number of patients with FMS pain, and secondly there was no homogeneity in the medication patients were using to treat their problem. However, by applying similar criteria for the designation of a successful treatment, it was permissible to incorporate all patients in the analysis. This is because in comparison to placebo, not only spontaneous pain but also the feeling of well-being significantly improved during therapy. And although the present study was not designed to provide a definitive comparison of the patient's usual medication for fibromyalgia, the amino acid/vitamin formulation produced significantly better pain relief when compared to placebo, keeping in mind that it was free of any side effects.

Conflict of Interest Statement

Authors are neither employed nor have financial and personal relationships or hold stocks of any company involved in marketing and/or sales of the amino-acid solution.

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