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Treatment of carpal tunnel syndrome with alpha-lipoic acid

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Abstract. – Carpal Tunnel Syndrome (CTS) is the most common peripheral mononeuropathy; its symptoms and functional limitations significantly penalize the daily activities and quality of life of many people. While surgery is reserved to most severe cases, the earlier stages of disease may be controlled by a pharmacological treatment aimed to "neuroprotection", i.e. to limiting and correcting the nerve damage.

Our study was aimed to compare the efficacy of a fixed association of α-lipoic acid (ALA) 600 mg/die and γ-linolenic acid (GLA) 360 mg/die, and a multivitamin B preparation (Vit B6 150 mg, Vit B1 100 mg, Vit B12 500 μg daily) for 90 days in 112 subjects with moderately se-vere CTS. Demographic, case-history and treatment efficacy data were collected; the Boston questionnaire was administered and the patients were evaluated by Hi-Ob scale and electro-myography.

A significant reduction in both symptoms scores and functional impairment (Boston ques-tionnaire) was observed in ALA/GLA group, while the multivitamin group experienced a slight improvement of symptoms and a deterioration of functional scores. Electromyography showed a statistically significant improvement with ALA/GLA, but not with the multivitamin product. The Hi-Ob scale showed significant efficacy of ALA/GLA in improving symptoms and functional impairment, while in the multivitamin group the improvement was significant, but less marked than in the ALA/GLA group.

In conclusion, the fixed association of ALA and GLA proved to be a useful tool and may be proposed for controlling symptoms and improving the evolution of CTS, especially in the ear-lier stages of disease.

Key Words:

Carpal Tunnel Syndrome, α-lipoic acid, γ-linolenic acid, Electromyography.

Introduction

The Carpal Tunnel Syndrome (CTS) is a neurological disorder characterized by pain, paresthesia and tingling, which are caused by a compression of the median nerve at the wrist level[1]. More frequently diagnosed between 30 and 50 with a female:male ratio of 3:1[2,3], the CTS is estimated to affect about 5% of adult population[4].

Treatment of CTS can be either surgical or medical. Surgery relieves the symptoms in most of cases, although the functional recovery may not be complete if the pre-operative damage of the nerve is severe[5]. Surgery is therefore reserved to the most severe cases with strength and sensitivity deficits or seriously altered electromyography or hypotrophy of the thenar[6].

During the earlier stages of disease, alternative non-pharmacological approaches can be followed, ranging from acupuncture and/or yoga to ultrasound, laser treatment or application of braces. Pharmacological treatments include either local steroid infiltrations or systemic administration of corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs), especially when synovitis is present; these drugs are needed to reduce the inflammation of the compressed nerve, although recent meta-analyses have not confirmed the efficacy of NSAIDs[7,8].

More effectively, the pharmacological treatment of CTS should be addressed to the "neuroprotection", i.e. to limiting and correcting the damage of the median nerve. In such a way, vitamin-based products have been proposed for CTS[9] and vitamin B_6 has been investigated in the treatment of CTS, although the results have been somewhat ambiguous as regards the improvement of symptoms[10]. Moreover, vitamin B complexes have been investigated in diabetic neu-

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ropathy as well as in alcoholic polyneuropathy, giving in some cases the evidence of beneficial effects on somatosensory symptoms[11,12].

The α-lipoic acid (ALA) has been proved effective in improving neuropathic symptoms and deficits of diabetic polineuropathy[13-16]. ALA works by means of different mechanisms, ranging from a powerful scavenging activity to a metabolic support of nerve cells, as well as to a modulation of neurotrophic cytokines release. All together, these mechanisms reduce inflammation, improve functioning of the nerve fibers and promote neuroprotection and neuroregeneration[17]. The SYDNEY II trial has assessed the efficacy of various oral doses of ALA, from 600 to 1800 mg/day for 5 weeks, in subjects with symptomatic diabetic neuropathy; the treatment led to a significant improvement of symptoms and a recovery of the neuropathic deficits and the dose of 600 mg/day demonstrated the best risk/benefit ratio[16].

Gamma-linolenic acid (GLA) is an essential fatty acid and a component of the cell membrane, from which inflammatory mediators are synthetized[18,19]; in particular, increased amounts of GLA modify the composition of the cell membrane, making it more fluid and improving the conduction of signals along the axons[20].

A formulation containing both ALA and GLA, which has been already proved effective in the treatment of disc-root conflict[21], has therefore drawn our attention and lead us to investigate it in the medical management of CTS. Although the initial causes of compression neuropathies, such as CTS and disc-root conflict, differ from those of diabetic neuropathy, all of them subsequently evolve by mechanisms involving an accumulation of free radicals and the consequent triggering of inflammatory processes.

Our study was therefore aimed to gathering information on the effects of this fixed association of ALA and GLA in patients with CTS, and to comparing it with a multivitamin B preparation.

Materials and Methods

The study consisted of collecting demographic, case history and treatment efficacy data, as well as information on the duration of disorder and any associated diseases. The Boston questionnaire[22] was administered before and after 90 days of treatment for subjective evaluation of night- and day-time pain, functional alterations and other characteristic symptoms of CTS, such as sluggishness, weakness and tingling. We have also performed an evaluation according to the Hi-Ob scale modified according to Giannini et al[23], which allowed the investigators to express an objective quantification of the modification of signs and symptoms characteristic of CTS, and an electromyography, the results of which are expressed according to a standardized scale for the electrophysiology of CTS[22]. The indication for surgery was also evaluated before and after treatment.

Two groups of 56 subjects were respectively treated with a fixed ALA based association (Alanerv, Alfa Wassermann, containing: ALA 300 mg, GLA 180 mg, Selenium 25 μg, Vit E 7.50 mg, Vit B_6 1.50 mg, Vit B_1 1.05 mg, Vit B_2 1.20 mg, Vit B_5 4.50 mg) at the dose of one capsule twice a day for 90 days, or with a multivitamin B preparation (Vit B_6 150 mg, Vit B_1 100 mg, Vit B_{12} 500 μg) at the dose of 3 capsules per day for 90 days. The use of any concomitant treatment, either indicated for CTS or for other co-existing diseases, was also recorded.

The baseline demographic and clinical data were summarized by means of frequency tables or central and dispersion tendency tables, using the most appropriate indicators for the actual distribution of the individual variables (mean, standard deviation, maximum and minimum value observed). The categorical type parameters were analyzed by applying the McNemar test and Fisher's exact test. For continuous type variables the Wilcoxon test was used, and for ordinal type parameters the sign test was applied. The variation over time of the parameters was analyzed and the statistical significance was evaluated. When necessary, the significance values were corrected for multiple comparisons. ANCOVA was used to assess whether the type of therapy caused a significant variation between the groups, adjusting for the baseline value of the relative parameter (covariate).

The degree of association between the trend of the Hi-Ob scale[23] and of the CTS electrophysiological scale[24] was measured by means of the Gamma Statistic that varies between -1 and 1. Values close to the absolute value 1 indicate a strong relationship between the two variables; values close to zero indicate little or no relationship. Cohen's K Statistic measured the agreement between the two scales evaluating the same patient. A value equal to 1 indicates perfect

agreement; a value equal to 0 indicates that the agreement can be considered casual. In cases where any data were missing, whatever the reason, no replacement approach was applied. The analysis faithfully describes the data collected.

The statistical analysis was performed using the SPSS Statistical Package software, ver. 13.0. p values < 0.01 were considered significant.

Results

The data analyzed refer to 112 subjects, 56 treated with ALA and 56 with a multivitamin B preparation.

Table I reports the demographic and clinical characteristics of the study population. It can be seen that the characteristics of the two groups were generally well balanced, the only exception being the significantly higher (p<0.001) percentage of newly diagnosed cases of CTS in the ALA group. Only in this group, and not in the multivitamin B group, were there subjects with associated diseases, the most frequent being hypertension (3/56) and diabetes (2/56). No subjects in either group were following associated treatment indicated for CTS, while in the ALA group several subjects were taking drugs for other diseases.

At baseline, no significant difference between groups was observed in the three assessment scales (subjective, objective and instrumental). However, the changes in the Boston CTS questionnaire scores observed with the two treatments during the study, seemed to reveal a better efficacy with ALA compared to the multivitamin product.

Figures 1 and 2 show the score changes for symptoms and functions, respectively, achieved in the Boston CTS questionnaire with the two treatments. The reduction of the scores in the ALA group was significant (p<0.001) in both the evaluations compared to the pre-treatment

Table I. Demographic and clinical characteristics of the study population. Results are expressed as mean ± SD and frequency as appropriate (between brackets, range and percentages). Statistically significant difference between treatments: *p<0.001.

	Total (n = 112)	ALA (n = 56)	Multivitamin B (n = 56)
Gender			
Female	95 (84.8%)	47 (83.9%)	48 (85.7%)
Male	17 (15.2%)	9 (16.1%)	8 (14.3%)
Age (years)*	50.2 ± 14.3 (18-85)	50.1 ± 15.6 (22-85)	50.3 ± 13.0 (18-75)
Weight (Kg)*	71.4 ± 9.8 (53-91)	73.1 ± 9.7 (55-91)	69.7 ± 9.7 (53-90)
Height (cm)*	166.0 ± 5.6 (150-180)	166.4 ± 6.3 (150-180)	165.7 ± 4.9 (160-178)
Carpal Tunnel Syndrome			
Blateral	54 (48.2%)	28 (50.0%)	26 (46.4%)
Right hand	44 (39.3%)	21 (37.5%)	23 (41.1%)
Left hand	11 (9.8%)	7 (12.5%)	4 (7.1%)
Not specified	3 (2.7%)	–	3 (5.4%)
Time to first diagnosis			
New diagnosis	15 (14.0%)	14 (26.9%)*	1 (1.8%)
1 to 12 months	33 (30.8%)	12 (23.1%)	21 (38.2%)
13 to 24 months	13 (12.1%)	6 (11.5%)	7 (12.7%)
25 to 48 months	17 (15.9%)	5 (9.6%)	12 (21.8%)
49 to 72 months	15 (14.0%)	8 (15.4%)	7 (12.7%)
More than 6 years	14 (13.1%)	7 (13.5%)	7 (12.7%)
Concomitant deseases			
Diabetes	2	2	–
Hypertension	3	3	–
Vascular disease	1	1	–
Thyroid nodule	1	1	–

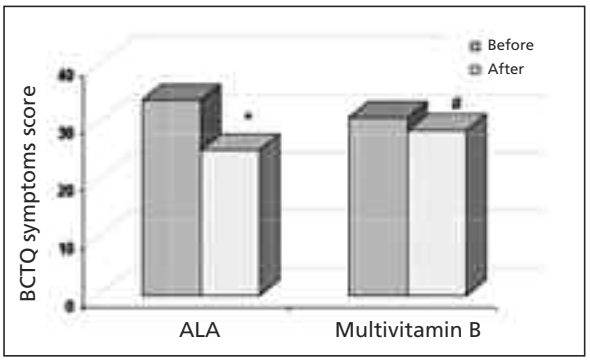

Figure 1. Boston Carpal Tunnel Questionnaire: Symptoms Score. Statistically significant differences versus baseline: **p*<0.001 at Wilcoxon's Test. #*p*<0.023.

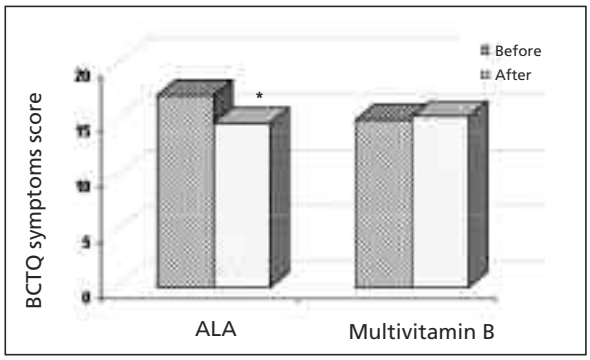

Figure 2. Boston Carpal Tunnel Questionnaire: Functional Score. Statistically significant differences versus baseline: **p*<0.001 at Wilcoxon's Test.

scores, while in the control group there were a slight improvement (p=0.023) in the symptom scores and a deterioration (p=0.037) of the function scores. For both scales (Figure 3), the therapeutic efficacy of ALA was significantly greater compared to the multivitamin B (p<0.001).

The electrophysiological assessment, also expressed as a score, showed a statistically significant improvement (p<0.001) in the group treated with ALA after 90 days, compared to the pre-treatment score, while the variation in the control group was not significant (Figure 4).

The analysis of the Hi-Ob scale (Figure 5) also showed significant (p<0.001) efficacy of ALA in improving the symptoms and functional impairment; with the multivitamin B the improvement of the Hi-Ob scale was not significant (p=0.016), but less marked than in the ALA group.

The evaluation of the degree of association between the variations observed in the Hi-Ob and electrophysiological scales showed a statistically significant concordance (p<0.001). This is important as it confirms that the treatment with ALA improves both the symptoms and the functional impairment of the damaged nerves.

In addition to evaluation by means of the Boston questionnaire, pain was assessed by asking the patients whether it was present or not. In the ALA group, it was found to be present in 83.9% of the subjects before treatment and in 39.3% after treatment, with a highly significant reduction (p<0.001). In the control group, the percentage of subjects with symptoms decreased, but the reduction was less marked: from 82.1% to 66.1% (p<0.004).

The indication for surgery was present in 76.8% of the subjects in the ALA group and 82.1% in the group treated with multivitamin B at time 0. After 90 days of treatment, this fell to 50% in the ALA group and to 69.6% in the control group. The improvement attributed to ALA with respect to the pre-treatment percentage was

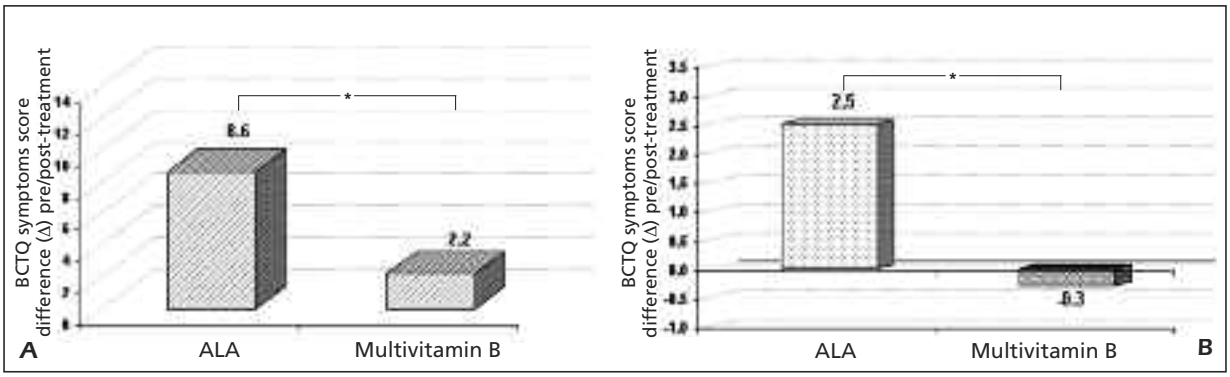

Figure 3. Boston Carpal Tunnel Questionnaire. Changes (∅) between pre- and post-treatment in the symptoms ***(A)*** and functional ***(B)*** scores (**p*<0.001; ANCOVA test, between the groups adjusting for the baseline value of the relative parameter).

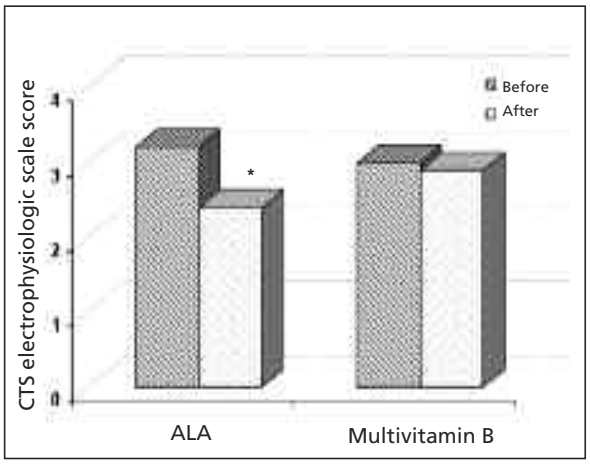

Figure 4. CTS Electrophysiologic Scale Score. Statistically significant difference versus baseline: *p<0.001.

statistically significant (p<0.001) and better as a trend, although not in statistical terms, compared to what was observed in the multivitamin B group.

No side events correlated with the two treatments were observed during the study.

Discussion

The results of this study suggest that a fixed association of ALA and GLA may be effective in improving symptoms and functional impairment in subjects affected by CTS. For most of the considered variables considered, there was a trend towards a better efficacy of the association ALA/GLA over the multivitamin B preparation administered as control group.

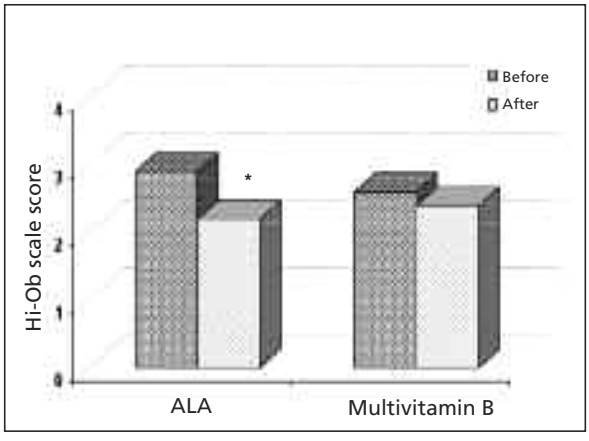

Figure 5. Hi-Ob Scale Score. Statistically significant difference versus baseline: *p<0.001.

Our study has obviously some limitations related to the "open" experimental design, the sample size and, last but not least, the characteristics of the population study. One of the problems in assessing the efficacy of medical treatments in CTS is the evaluation of symptoms and functional impairment, since it is necessary to take into account the subjective perception of the symptoms of affected subjects. However, it is equally important to have objective assessment parameters that can be used to follow the evolution of the disorder and on the basis of which surgery can be prescribed in the more advanced stages.

This is why, in evaluating the efficacy of the treatment in our study, we used three different scales that take all aspects into account. The application of three different criteria in evaluating the efficacy of the treatment – subjective, objective and instrumental – balances out the limitations of the experimental design and the size of the sample.

The concordance on the trend of the results for all three efficacy evaluation criteria reinforces the quality of the final results. The group treated with ALA had a statistically higher percentage of newly diagnosed cases of CTS, but this does not appear to represent a limitation to interpretation of the results, since the severity of the symptoms and functional impairment at the pre-treatment examination was similar in the two groups.

The treatment with ALA led to a significant improvement of the score relative to the symptoms and residual function, calculated on the basis of the Boston CTS questionnaire which records the subjective perception of those affected by CTS, according to standardized criteria. This is an important result as it is precisely these symptoms that penalize activities and reduce the quality of life.

The treatments used in CTS include some that are effective in relieving the symptoms and others that act mainly on the functional impairment of the affected limb. The administration of ALA led to variations in the scores of the Hi-Ob scale and of the electrophysiological scale, which showed a statistical concordance. In addition, the reduction in the percentage of subjects with pain and of those in whom surgery had been indicated was more marked in the ALA group. Considered together, these results indicate that the ALA/GLA association produces effects that are not limited to the correction, disappearance or re-

duction of the symptoms, but which modify the physiopathology of CTS more profoundly.

How a fixed association of ALA and GLA works in patients with CTS is matter of speculation.

CTS is characterized by damage to the median nerve caused by compression of the nerve by the transverse ligament, and it evolves through inflammatory and neurodegenerative phenomena. ALA and GLA have demonstrated pharmacological effects that can be important in countering the inflammation of the nerve fibers and in promoting neuroprotection and neuroregeneration. Oxidative stress appears to play a crucial role in peripheral neuropathies with a metabolic basis[10]. However, also in inflammatory forms caused by mechanical compression the accumulation of free radicals can trigger vicious circles that perpetuate the damage and prevent remission[25,26].

The administration of ALA has been proposed in many disorders characterized by chronic oxidative stress[27]. In particular as far as nerve damage is concerned, it has been shown to reduce lipid peroxidation of the peripheral nerves and the central nervous system; to normalize the production of nuclear transcription factors, such as NF-κB, caused by the accumulation of free radicals; to improve local blood flow; to increase oxygen absorption and to improve the metabolic equilibrium of the nerve structures in general, as well as improving the conduction velocity of the nerve stimulus and reinforcing the neuroprotection mechanisms[17].

Furthermore, the administration of GLA can correct the lack of this fatty acid that occurs in neurodegenerative processes and reduces the production of inflammation mediators in the axons. Through its conversion to PGE1, GLA has anti-inflammatory, antithrombotic, antiproliferative and lipid-lowering effects, as well as causing relaxation of the muscle fibers. It also has the important effect of re-establishing and maintaining a correct membrane fluidity[18-20]. The combined administration of the two molecules has been shown to develop a positive synergy in some peripheral neuropathies[28,29] and in disc-root conflict neuropathy[21].

In conclusion, the fixed association of ALA and GLA proved to be a useful tool in controlling the symptoms and improving the evolution of CTS, especially in the earlier stages of disease. This product is therefore proposed for controlling the symptoms of CTS and improving the evolution of the clinical situation.

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