THE USE OF ALPHA-LIPOIC ACID (ALA), GAMMA LINOLENIC ACID (GLA) AND REHABILITATION IN THE TREATMENT OF BACK PAIN: EFFECT ON HEALTH-RELATED QUALITY OF LIFE

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The aim of this trial was to evaluate the effects of α-lipoic acid (ALA) and γ-linolenic acid (GLA) and the beneficial effect of physical exercise on positive sensory symptoms and neuropathic pain in patients with compressive radiculopathy syndrome from disc-nerve root conflict. Often these painful syndromes after the acute event, tend to recurrence becoming subacute or chronic syndromes that become for the period of interest disabiling is an event very important in these cases proper prevention, based on a maintenance drug therapy and the strengthening exercises of paravertebral muscles, flexibility exercises on the spine and when needed on the reduction of body weight. In this Observational Cohort, two-arm trial, 203 patients were enrolled and divided into two groups, the first, "ALA and GLA group", (n = 101) received oral dose of 600 mg of α-lipoic acid (ALA) and 360 mg of γ-linolenic acid (GLA) and a rehabilitation program for six weeks , the second (n = 102) treated with only rehabilitation program. Patients were recruited at the centre of Physical Medicine and Rehabilitation, have undergone a physiatric examination at the primary outcome (t_0) and secondary outcomes were recorded at monitoring visits scheduled at two weeks = t_1, four weeks = t_2, six weeks = t_3, and at the same has been administered the following scale: VAS scale, SF-36, Oswestry Low Back Pain Disability Questionnaire, Aberdeen Back Pain Scale (ABPS), Revised Leeds Disability Questionnaire (LDQ), Roland and Morris Disability Questionnaire. Significant improvements has been noted in the "ALA and GLA group" for paresthesia, stabbing and burning pain, as showed by VAS (Visual Analogue Scale), Oswestry Low Back Pain Disability Questionnaire, Aberdeen Low Back Pain Scale; also, improvements of "quality of life" has been noted, in the same group, as showed by SF-36, LDQ (Revised Leeds Disability Questionnaire), Roland and Morris disability questionnaire. These all outcome measure showed decreases statistically significant. Oral treatment with α-lipoic acid (ALA) and γ-linolenic acid (GLA) for six weeks in synergy with rehabilitation therapy improved neuropathic symptoms and deficits in patients with radicular neuropathy.

Radicular pain is a form of neuralgia due to an irritation of sensory root or the dorsal root ganglion (DRG) of spinal nerve. (1) An important percentage of painful syndromes are due to compression of nerve roots from "disc root conflict". It's a complex problem because the causes may be different. In 80% of back pain the origin of pain is a disease of the intervertebral disk, that can be corrupt and degenerate in various ways and to varying severity, up to hernia. Radicular pain should not be confused with radiculopathy. Radiculopathy is objective loss of sensory and / or motor function as a result of conduction block; the features of which might include paresthesia, numbness, stabbing and burning pain, motor loss, wasting, weakness and loss of reflexes.(2), (3). Any lesion that affects the integrity of the nerve root can cause radicular pain, radiculopathy or both. (1)

Pain does not follow the corresponding dermatomes and it is the sensory loss that indicates the affected segment. For example, lumbar radicular pain travels through the lower limb along a narrow band usually not more than 5-8 cm wide, and when experimentally reproduced, the perceived pain is qualitatively sharp, shooting or lancinating.(5). Back pain is a frequent symptom, which can be accompanied by pain at upper limb and lower limb (low back pain). A serious problem for patients with spinal pain is considerable limitation in the range of movement of the trunk and pelvis,

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often accompanied by shortening of the hamstring tendons and limitation of flexion or extension in the coxofemoral joint.(6-10). Often these painful syndromes after the acute event, tend to recur becoming subacute or chronic syndromes that become a disabling event.This exerts a important impact on the quality of life, causing interference of sleep and enjoyment of life. Neuropathic diseases are subjective symptoms of major clinical importance then often motivates patients to seek health care.(12-13).

Chronic spinal pain is the most common cause of long term disability in middle age and is resistant to treatment, and patients are often referred for multidisciplinary treatment.(14). Estimates suggest that 80% of all adults will experience some degree of back pain in a given year, and 30% of the population will seek treatment for this problem.(11). The economic effects of spine disorders is great. Spine disorders rank fifth among disease categories in the cost of hospital care and account for higher costs resulting from absenteeism from the work and disability than any other category. The scientific basis for the various conservative treatments used in this pathology is weak, however, it is a general opinion that drugs therapy (paracetamol, tramadol, non-steroidal anti-inflammatory drugs – NSAIDS- myorelaxant, steroids, antidepressants) and physical exercise (aerobic work, Back Scool, Mc Kenzie) play an important role in the treatment of patients with back pain. (17).

Recent studies showed that treatment with α-lipoic acid reduces the pain, paresthesia, and numbness in symptomatic diabetic polyneuropathy. (12), (13). The antioxidant metabolic α -lipoic acid is a substance with low molecular weight that is introduced into the diet and can cross the blood-brain barrier, is metabolized in cells and reduced acid dehidrolipoic, which is also exported in the extracellular space, ensuring protection both intra and extracellular. Both α -lipoic acid that (and especially) the dehidrolipoic are powerful antioxidants that can regenerate other antioxidants such as vitamins C and E, and to increase the levels of intracellular glutathione.

Recents study shows α-lipoic acid restores endothelial function and significantly improves systemic and local oxidative stress in high-fat fed GK diabetic rats. Improved endothelial function due to α-lipoic acid was at least partially attributed to recoupling of eNOS and increased NO bioavailability and represents a pharmacological approach to prevent major complications associated with type 2 diabetes. (18). It seems therefore be an ideal product for the treatment of brain and neural disorders, especially in the presence of free radicals.(19)

An examination of modern research note protective action in cerebral ischemia, in some brain damage in mitochondrial dysfunction in diabetes and diabetic neuropathy, congenital and metabolic dysfunction in many other causes of pathological conditions acute or chronic charged to the brain and nerve tissue. Many trials conduced in vitro human tissues and animals, indicate that α -lipoic acid may have a significant effect in many neurodegenerative disorders. Recents trials show the possible prophylactic role of dietary gamma-lynolenic acid (GLA), as one interesting dietary approaches, in treating various chronic disease states.

γ-linolenic acid (GLA) is an essential omega-6 fatty acid, is a precursor of a prostaglandin Inibits at the cellular level, the E2 prostaglandin that inhibits the synthesis of nitrogen monoxide with a consequent stimulation of the type 2 reactions and the production of antibodies. So this prostaglandin must be inhibited. The dietary GLA increases the content of its metabolic product the DGLA dihomo-gamma-linolenic acid, within cells membranes without concomitant changes in arachidonic acid. So the mechanism can be summed up in an anti-inflammatory and antiproliferative. Therefore it was conducted an observational trial comparing the recovery of any inconvenience resulting from back-pain from disc-root conflict in two groups of subjects undergoing rehabilitation treatment, where one group received a daily drug supplement, throughout the year of the study, with ALA and GLA

RESEARCH DESIGN AND METHODS

The aim of this study was evaluate the effects of α-lipoic acid (ALA) and γ-linolenic acid (GLA) ALA and GLA complex in synergy with rehabilitation therapy on positive sensory symptoms and neurophatic deficits in patients with compressive root syndromes from conflict disk root

It was conducted an observational two arms trial, enrolling 203 subjects with back-pain and related symptoms, including subjects relating at the Physical Medicine and Rehabilitation Unit. The first arm, group A "ALA and GLA" composed of 101 patients was treated with oral dose of 600 mg of α-lipoic acid (ALA) and 360mg of γ-linolenic acid (GLA) and undergo a rehabilitation program for a period of 6 consecutive weeks, while the second leg, group B, composed of 102 patients were subjected only to dedicated rehabilitation program for 6 weeks.

They are applied to the trial 247 patients; only 216 (87.45%) were enrolled answering the inclusion criteria (Table 1), 13 patients (6%) were excluded during the follow-up since they have not completed the trial, of which 7 (2%) were lost from group A which received drug supplementation (ALA-GLA group) and 5 (2%) from group B. Drawing attention that a person (0.5%) stopped because of adverse reactions to an excipient (polyvinylpyrrolidone) showing a skin rash in thoraco-abdominal region, cetirizine dihydrochloride treated at a dose of 10 mg orally.

The characteristics of those enrolled person are defined in Table 2.

Eligible patients in treatment have been subjected to recruitment (t0), at two weeks (t1), four weeks (t2), six weeks (t3),to a physiatric examination and administration of the following scale as outcome measures: VAS (Visual

Table I

INCLUSION CRITERIA	EXCLUSION CRITERIA
18 to 75 years of age patients Radiologically confirmed disc herniation Subacute and/or chronic radicular sindrome	Cauda equine syndrome Muscle paralysis Insufficient strength to move against gravity Acute episode with similar signs and symptoms during the previous 12 months Previous spine surgery Bony stenosis Spondylolisthesis Pregnancy Severe coexisting disease Low back pain in patients with S.M. Coagulation desease Cardiovascular disease Rheumatic disease Hepatic failure Adverse Drug Reactions

Table II

Characteristics of the Patients	Group A ALA-GLA+FKT (n=101)	Group B Only FKT (n=102)
Age – yr	56.1	52.9
Male sex – no.(%)	44 (44)	40 (39)
Body-mass index	32	30
Smokers – no.(%)	34 (34)	40 (39)
Duration of radicular syndrome – wk	25	23
Took sick leave from work – no.(%)	19 (19)	16 (16)
Radiating pain in legs – no.(%)	46 (46)	48 (47)
Radiating pain in arms – no.(%)	12 (12)	15 (15)
Pain on straight leg raising – no.(%)	5 (5)	8 (8)
Pain on crossed straight leg raising – no.(%)	9 (9)	6 (6)
Sensory loss – no.(%)	21 (21)	16 (16)
Dermatome anesthesia – no.(%)	5 (5)	6 (6)
Muscle weakness – no.(%)	62 (61)	57 (56)
Difference in deep tendon reflexes in the kness – no.(%)	19 (19)	17 (17)
Difference in deep tendon reflexes in the foot – no.(%)	22 (22)	22 (22)
Difference in deep tendon reflexes in the elbow –no.(%)	11 (11)	15 (15)
Difference in deep tendon reflexes in the wrist – no.(%)	7 (7)	9 (9)

Analogue Scale), SF-36, Oswestry Low Back Pain Disability Questionnaire, Aberdeen Back Pain Scale (ABPs), Revised Leeds Disability Questionnaire (LDQ), Roland and Morris Disability Questionnaire.

The purpose of our trial was to compare the two treatment groups, considering that main variable, the degree of disability in performance of activities of daily living, by the scores obtained by the Roland disability questionnaire, the VAS scale, the SF-36 scale, the Oswestry scale, the ABPs scale and LDQ scale, this for the low-back-pain.

The Roland Disability Questionnaire is a disability-specific disease scale that measure functional status in patients with legs or back pain: the score ranging from 0 to 23.

The pain intensity is measured with a visual-analogue scale (VAS), where 0 is no pain and 10 the worst pain ever felt.

The SF-36 is a generic questionnaire on health status, which consists of 36 items relating to physical and social conditions, divided into eight domains of quality. The score ranging from 0 to 100, indicating less severe symptoms for gradually increasing values.

The Oswestry Low Back Pain Disability Questionnaire is an important tool that measures the functional disability and the limitation that it comes in the activities of daily life. The ABPs Scale consists of 19 questions about pain, the aggravating factors, distribution of symptoms and effects of pain on functions. The score ranges from 0 to 100.

The LDQ is a self-questionnaire that measures the residual function and disability, and investigating 4 major aspects: mobility, bending, posture and movements of the neck. The score ranges from 0 to 48, the minimum scores indicate less functional disability.

STATISTICAL ANALYSIS

The data collected during treatment have been processed by the t-student statistical test for paired samples, considering the average difference of the variation of the numerical parameters of each assessment scale administered before and after treatment.

RESULTS

Patients in both groups reported statistically significant results, this data points out that the group that

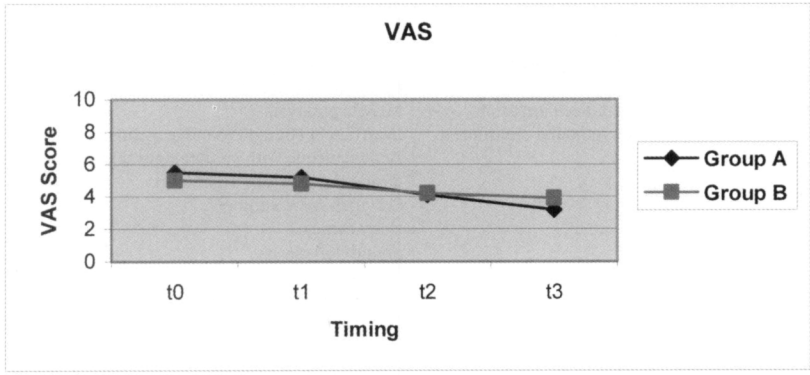

Fig. 1: *P<0.0005 T_3 vs T_0 group A, P<0.005 t_3 vs t_0 group B, P<0.05 t_3 group A vs group B. Values of pain intensity measured on the visual-analogue scale (VAS), at the time T_0, T_1, T_2, T_3 enrolled in the two groups, developed with the test statistic for t-student paired samples, which show for the group that took ALA-GLA (Group A) an early response to increase the threshold of pain.*

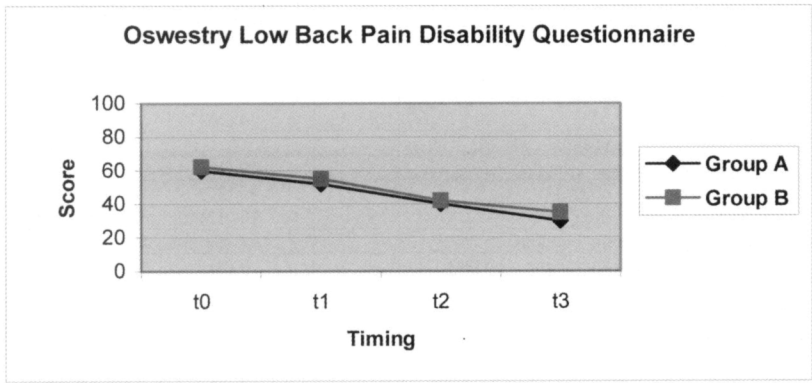

Fig. 2: *P<0.0005 T_3 vs T_0 group A, P<0.005 t_3 vs t_0 group B, P<0.05 t_3 group A vs group B. Measurement of functional disability and the limitation that it derives from activities of daily living, at the time T_0, T_1, T_2, T_3 enrolled in the two groups, developed with the test statistic for t-student paired samples that showed a direct correlation better pain modulation exerted by the administration of ALA-GLA in subjects of Group A.*

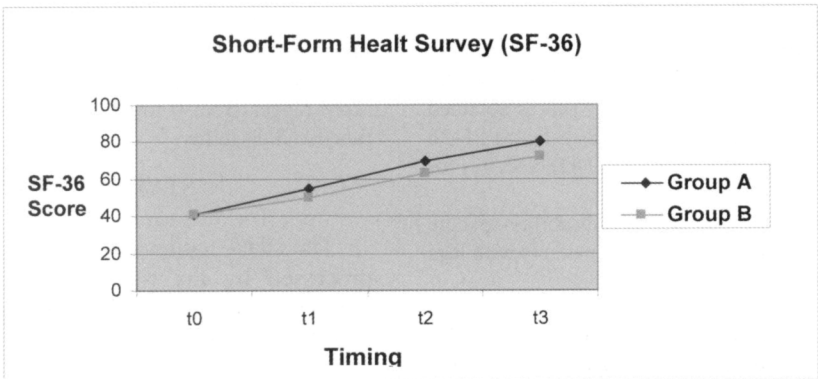

Figure 3: *P<0.0005 T_3 vs T_0 group A, P<0.005 t_3 vs t_0 group B, P<0.05 t_3 group A vs group B. Measurement of health status (consists of 36 items relating to physical and social conditions, divided into eight domains), at the time T_0, T_1, T_2, T_3 enrolled in the two groups, developed with the test statistic for t-student paired samples, which shows a gradual increase of the linearity test, dissertation on a better quality of life in ADL and social context, in the two groups enrolled in percentage terms but greater in Group A.*

took ALA-GLA has shown a greater significance with respect to all assessment scales, by calculating the values of t> t critical and having a significance equal p <0.0005, at a rate equal to 75% of patients. The group treated with only rehabilitation therapy, has provided results with significance equal p <0005, showing a statistically lower answer than in group A, with respect to the total score of the rating scales SF-36, Oswestry, Roland and Morris.

The parameters obtained by statistical analysis have revealed a greater reduction in pain, improved the mood and tone of a better quality of life.

The subjects who received supplementation with ALA and GLA had response rate significantly higher than the group subjected only re-education treatment. In fact, patients in group A showed a more precocious answer in the pain threshold raising (Figure 1) and sustained over time, with an end-point of the study by approximately 75%.

Raising and modulation of pain threshold are related to the assessment scale of the disability degree and quality of life, especially for the Oswestry Low Back Pain Disability Questionnaire and SF-36 (Figure 2 and Figure 3).

As with any clinical trial should be noted that the proposed clinical therapeutic-rehabilitative approach should be monitored over time to see the improvements achieved, in time that is the expected results, are then maintained over time, especially in the prevention of recurrence, welded to a chronic pathology in most of patients enrolled, and not devoid of future deterioration in terms of anatomical pathology.

CONCLUSIONS

In the study - Irbesartan and lipoic Acid in Endothelial Dysfunction (ISLAND)-, oral administration of 300 mg / day of ALA alone and in combination with irbesartan (150 mg / day) in patients with metabolic syndrome has resulted in a significant increase in the endothelium-dependent flow-mediated brachial artery vasodilatation 44 and 75% respectively, compared to treatment with placebo after 4 weeks.

This effect was accompanied by reductions of interleukin-6 and the plasminogen activator inhibitor type-1 in plasma level, suggesting that drug could improve the endothelial dissemination through antithrombotic and anti-inflammatory mechanisms (25).

The mechanisms of the rapid improvement of symptoms is that neuropathic deficits in the disc-root conflict, may be related to improved blood flow of the vasa nervorum mediated by antioxidant ALA (26-34) and GLA anti-inflammatory and antiproliferative action, with favourable influence on inflammation mechanisms to load the myelin of peripheral nerve fibers but also the structures of the disc. (4)

The results of the trial demonstrate that oral treatment with 6 consecutive weeks oral dose of 600 mg of α-lipoic acid (ALA) and 420 mg of γ-linolenic acid (GLA) associated with a rehabilitation program improved the neurophatic symptoms and deficits in patients with radicular syndrome from disc-nerve root conflict.

The authors intent to continue the study by long-term monitoring changes of the results obtained, in order to better understand how it can be adjusted the weight of disability in a very frequent and chronic progressive problem.

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