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FULL COMMUNICATION

Effect of Alpha-Lipoic Acid on Clinical and Neurophysiologic Recovery of Carpal Tunnel Syndrome: A Double-Blind, Randomized Clinical Trial

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ABSTRACT The objective of our study was to examine the effect of alpha-lipoic acid (ALA) on clinical and neurophysiologic outcomes after surgery for idiopathic carpal tunnel syndrome (CTS). We conducted a randomized, double-blind, placebo-controlled clinical trial in 20 adults diagnosed with idiopathic CTS after clinical and neurophysiologic assessment. Eligible participants took 600 mg ALA or placebo per day for 1 month before surgery, and for 2 months afterward. Further clinical and neurophysiologic assessments were undertaken immediately before surgical decompression, and at 12 weeks postoperatively with additional clinical assessments at the 4th and 8th week after surgery. Clinical outcome measures were taken by Boston Questionnaire score, the presence or absence of Tinel's sign, and Phalen's test findings. Median nerve conduction studies were also undertaken and interpreted according to Dumitru's reference values. Nineteen patients completed the study; one member of the placebo group was lost during follow-up. There were significant improvements in clinical and neurophysiologic variables in the ALA treatment group, present even before surgery. Boston Questionnaire scores had improved significantly in both groups. In the ALA group, none of the participants had positive Phalen's or Tinel's signs at 12 weeks, and motor and sensory fiber latency and amplitude had significantly improved; in the placebo group, only the sensory distal latency had improved significantly. In conclusion, ALA administered 1 month before open decompression and for 2 months afterward improves the clinical and neurophysiologic outcomes after surgery.

KEYWORDS: • ***alpha-lipoic acid*** • ***carpal tunnel syndrome*** • ***ischemia/reperfusion*** • ***neuroprotection***

INTRODUCTION

CARPAL TUNNEL SYNDROME (CTS) is the most common compressive neuropathy in adults, with an incidence in both genders of 376 per 100,000 U.S. habitants combined[1] and with a prevalence that usually varies in relation to the risk factors; a study among poultry processing employees reported an estimated prevalence of 42%.[2] The symptoms are caused by compression of the median nerve at the wrist. Clinical features include numbness among the distribution of the median nerve, pain and atrophy of the thenar eminence may develop in more advanced stages. The risk of CTS appears to be elevated in individuals who adopt long periods of extreme flexion/extension wrist postures, most likely due to their occupation.[3]

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The symptoms of CTS are caused by increased pressure within the carpal tunnel, and therefore, a decreased function of the median nerve.[4] Nerve damage is attributed to restriction of blood flow in the endoneural capillary system, which induces alterations in the blood/nerve barrier structure, provoking an endoneural edema, venous congestion, ischemia, and subsequent metabolic abnormalities.[5,6] It has been proposed that ischemia/reperfusion injury of the median nerve results in oxidative stress and inflammation of the subsynovial connective tissue, which play an important role in the evolution of idiopathic CTS.[7,8]

Patients with mild or moderate CTS may first be offered conservative treatment. Options include splinting,[9] corticosteroid therapy,[10] physical therapy, and therapeutic ultrasound.[11,12] Patients with severe CTS and those whose symptoms have not improved after 4–6 months of conservative therapy should undergo surgical decompression. Endoscopic or open techniques are equally effective.[13] Clinical and neurophysiologic improvements can be observed within the first 3 months of surgery, but up to 20% of

patients may experience persistent postoperative sensory symptoms.[14,15]

Other studies have provided evidence suggesting that alpha-lipoic acid (ALA) and other antioxidants exhibited neuroprotective effects in an experimental model of nerve compression.[16,17] Di Geronimo *et al.*,[18] Pajardi *et al.*,[19] and Notarnicola *et al.*[20] have reported that a combination of ALA and other antioxidants can improve the clinical symptoms of CTS. ALA is a natural thiol and its reduced form, dihydro-lipoic acid, has been called the ''universal antioxidant,'' which is able to regenerate endogenous antioxidants such as vitamins C and E, and regulate the transcription of genes associated with antioxidant and anti-inflammatory pathways. ALA exists as two different enantiomers: the biologically active (R)-isomer and the synthetic (S)-isomer. Vegetable and animal tissues contain low amounts of R-ALA detected in the form of lipoyllysine (ALA attached to a specific lysine residue). The most abundant vegetable sources of R-ALA are spinach, broccoli, and tomatoes. In animal tissues, the highest concentration of lipoyllysine is found in the kidney, heart, and liver. Thioctic acid is used worldwide as a nutraceutical or registered drug, and it is marketed mainly in the racemic thioctic acid form (50/50 mixture of R-ALA and S-ALA) for stability reasons.[21]

The aim of this study was to evaluate the effect of adjuvant ALA monotherapy to enhance the clinical and neurophysiologic improvement of surgical decompression in patients with idiopathic CTS.

MATERIALS AND METHODS

A randomized, double-blind, placebo-controlled clinical trial was conducted in 20 adults diagnosed with idiopathic CTS according to the American Association of Neuromuscular and Neurodiagnostic Medicine criteria between March 2015 and June 2016. The protocol was approved by the Local Bioethics Committee of the Health Sciences University Center (CUCS) of the University of Guadalajara (reference number 265/14) and registered as a clinical trial online (ClinicalTrials.gov: NCT02382328) before patient enrollment.

We excluded patients who had taken any neuroprotective or antioxidant drugs within the past 3 months. Other exclusion criteria were as follows: pregnancy, diabetes mellitus, hypothyroidism, rheumatoid arthritis, polyneuropathy, radiculopathy, Colles' fracture, Martin–Gruber anastomosis, and an allergy to ALA. All eligible patients provided written informed consent to participate. Patients who declined surgery or were lost during follow-up were excluded from the analysis.

Patients were enrolled and underwent surgery at the Hospital Civil of Guadalajara ''Fray Antonio Alcalde,'' in Guadalajara, Jalisco, México. Clinical and neurophysiologic assessments were undertaken at the University of Guadalajara at baseline (diagnosis); immediately before surgery (4 weeks after baseline); and then 12 weeks after surgery. Two additional clinical assessments were undertaken at the

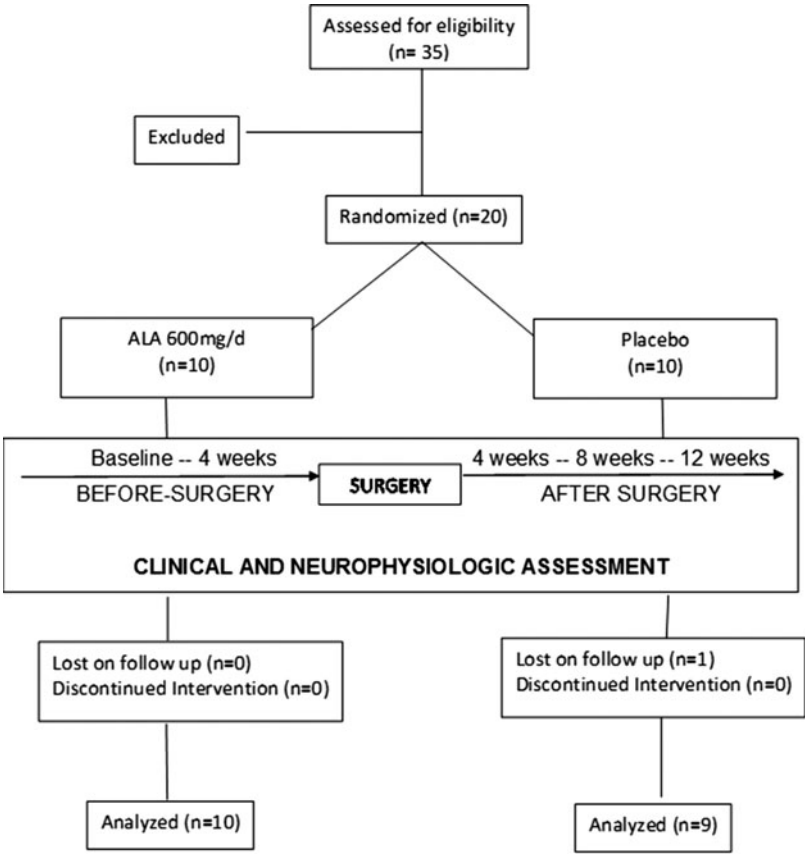

FIG. 1. Consort diagram.

Table 1. Characteristics of the Population

	ALA (n = 10)	*Placebo (n = 10)*	P
Age (years)	45.3	48.4	.52
Symptom duration (months)	15.2	13.6	.76
Male/female (*n*)	1/9	1/9	1.00
Occupation (professional/home) (*n*)	7/3	4/6	.17
Affected side R/L	6/4	8/2	.32

ALA, alpha-lipoic acid; R, right; L, left.

4th and 8th week after surgery. The 12th week assessment was the final assessment.

Clinical evaluation

Two clinical provocation tests were performed. Phalen's test was performed by tapping over the median nerve as it passes through the carpal tunnel; a positive response was defined as a sensation of tingling in the distribution of the median nerve in the hand. Tinel's test was performed by hyperextending the wrist for 60 sec; a positive response was defined as a sensation of tingling in the distribution of the median nerve over the hand.[3] A validated version of the 11-item Boston Questionnaire for CTS in Spanish (score range 11–55) was completed by participants at each assessment to assess symptom severity.[22]

Electrophysiology

Nerve conduction studies were performed at baseline, immediately before surgery, and the final assessment at 12 weeks by a certified rehabilitation medicine specialist using Viking™ software on Nicolet® EDX equipment (Natus, Pleasanton, CA, USA). Electrophysiology recordings from the median nerve were considered in the context of Dumitru's reference values: distal sensory latency 3.0 ± 0.3 ms, distal sensory amplitude 15–50 μV, distal motor latency 4.2 ms, and distal motor amplitude 13.2 ± 5 mV.[23]

Drug administration schedule

Treatments were assigned following a simple randomization procedure using sealed envelopes. The labeling and coding of the bottles were made and maintained by an independent researcher. Physicians, surgeons, participants, and investigators were unaware of the treatment allocation until the end of the analysis. All patients received general recommendations about how take the drug. Ten patients took 600 mg of racemic ALA (mixture of 50/50 of R and S enantiomers) once daily before food, and the other 10 subjects received a placebo (calcinated magnesia) of identical pharmacologic presentation (VIDRIO Pharmaceutical Company, Guadalajara, Mexico). Participants took the study drug or placebo for 4 months (for 1 month preoperatively and 3 months postoperatively). Four subsequent visits were scheduled to guarantee compliance (personal diary and medication counting) with treatment, to supply the medication, and to measure outcomes.

Surgery

A certified plastic and reconstructive surgeon unaware of participants' group allocation undertook open surgical decompression at the Civil Hospital of Guadalajara. After surgery, a soft bandage was applied and 7-day courses of ketorolac and clindamycin were prescribed to all patients.

Statistical analyses

Data are presented as mean and standard deviation for parametric variables and number (proportion, %) for non-parametric variables. The Shapiro–Wilk test was used to evaluate normal distribution, and intra- and intergroup differences were tested using the Friedman test; also, a Wilcoxon signed-rank test was applied to compare two times separately. Qualitative variables in each group were analyzed using Fisher's exact test. A P-value $\leq .05$ was considered statistically significant. SPSS software was used for all statistical analyses (version 21.0; IBM, Armonk, NY, USA).

RESULTS

Twenty patients were enrolled in the study and 19 (95.0%) completed it. One participant in the placebo group was lost during follow-up (Fig. 1). The baseline demographic and clinical characteristics of the study are shown in Table 1; there were no statistically significant differences between the ALA and placebo groups.

Table 2. Clinical and Neurophysiologic Findings at Preoperative Assessment After 4 Weeks of Study Drug Administration

	ALA group			*Placebo group*		
Clinical and neurophysiologic variables	*Baseline*	*Before surgery*	P	*Baseline*	*Before surgery*	P
Distal sensory latency (ms)	4.42 ± 1.8	4.10 ± 1.6	**.01**	4.22 ± 0.5	4.09 ± 0.4	.17
Sensory amplitude (μV)	9.09 ± 7.8	11.79 ± 8.2	.39	19.39 ± 7.5	18.33 ± 6.8	.15
Distal motor latency (ms)	6.16 ± 1.3	5.04 ± 1.0	**<.01**	5.04 ± 0.8	4.75 ± 0.9	.16
Motor amplitude (mV)	5.9 ± 3.0	6.63 ± 2.8	**.04**	7.08 ± 2.6	6.46 ± 2.0	.17
Boston Questionnaire	37.1 ± 9.7	26.8 ± 11.5	**<.01**	38.1 ± 10.9	35.25 ± 14.5	.20
Tinel's sign (*n*)	9	2	**<.01**	8	7	.42
Phalen's test (*n*)	10	1	**<.01**	8	8	1

The bold values indicate statistically significant changes.

Table 3. Clinical and Neurophysiologic Findings at Final Assessment 12 Weeks After Surgery

	ALA group			*Placebo group*		
Clinical and neurophysiologic variables	*Baseline*	*Final*	P	*Baseline*	*Final*	P
Distal sensory latency (ms)	4.42 ± 1.8	3.30 ± 1.3	**<.01**	4.22 ± 0.5	3.68 ± 0.1	**<.05**
Sensory amplitude (μV)	9.09 ± 7.8	15.82 ± 9.5	**<.01**	19.394 ± 7.5	23.97 ± 7.5	.16
Motor distal latency (ms)	6.16 ± 1.3	4.86 ± 1.0	**<.01**	5.047 ± 0.8	4.27 ± 1.0	.11
Motor amplitude (mV)	5.9 ± 3.0	7.04 ± 2.09	.074	7.08 ± 2.6	6.86 ± 1.9	.76
Boston Questionnaire	37.1 ± 9.7	12.6 ± 1.7	**<.01**	38.1 ± 10.9	18.56 ± 8.1	**<.01**
Tinel's sign (*n*)	9	0	**<.001**	8	2	.211
Phalen's test (*n*)	10	0	**<.001**	8	1	.474

The bold values indicate statistically significant changes.

After the intervention with ALA, there were significant improvements in sensory and motor latency ($P < .001$) and in motor and sensory amplitude ($P < .01$), with a slight improvement of the placebo group in distal sensory latency ($P = .08$) and distal motor latency ($P = .07$) without any significant results.

Immediately before surgery, after 1 month of treatment, there were significant improvements in sensory and motor latency and motor amplitude in the ALA group; however, there were no significant changes in the placebo group (Table 2). After 1 month of ALA treatment, the preoperative Boston Questionnaire score had fallen significantly, still with no significant changes in the placebo group. Over the same period, there were also significant reductions in the number of patients with a positive Tinel's sign (90.0% at baseline compared with 20.0% preoperatively) and in whom Phalen's test was positive (100% at baseline compared with 10.0% preoperatively); however, there were no significant changes in the placebo group (Table 2).

Neurophysiologic results obtained 12 weeks after surgery in the ALA group showed significant improvements in all parameters studied; median nerve sensory and motor latency and amplitude (Table 3). Subjects in the placebo group exhibited significant reduction in distal motor latency, but there were no significant changes in any of the other neurophysiologic variables (Table 3). Clinical variables showed significant improvements in both groups at the final assessment. Tinel's sign was absent and Phalen's test was negative at the final assessment 12 weeks after surgery in all participants in the intervention group, however, two patients had a positive Tinel's sign (22.2%) and one participant had a positive Phalen's test (11.1%) in the placebo group. The Boston Questionnaire score had improved significantly in both groups at the final assessment (ALA group, $P = .005$; placebo group, $P = .008$). Subjects in the ALA group reported lower scores from postoperative week 8, while those in the placebo group showed improvement until postoperative week 12 (Fig. 2).

DISCUSSION

We found that an oral 600 mg daily dose of ALA for 1 month before surgery and 3 months after surgery improved clinical and neurophysiologic outcomes after open decompression of idiopathic CTS. Ours is one of the first clinical

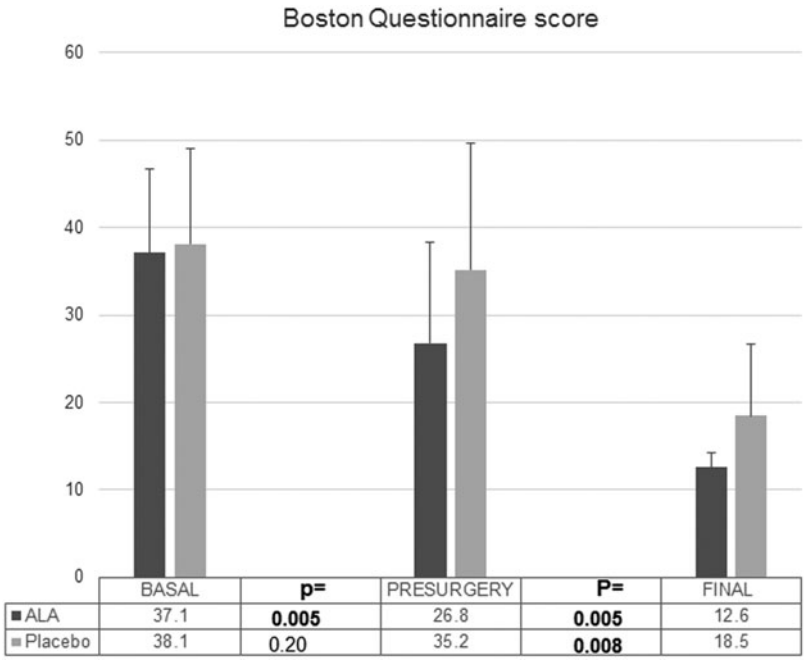

FIG. 2. Changes in Boston Questionnaire score over the study period.

trials, publicly registered, of perioperative ALA monotherapy in CTS, and the only study to our knowledge that used ALA before and after surgery.

In the nervous system, ALA is reported to have neuroprotective and antioxidant effects in experimental and clinical studies.[16,24–26] Senoglu *et al.*[16] have demonstrated the actions of ALA in models of compressive sciatic nerve injury in rats. They found that ALA reduces oxidative stress by increasing the activities of catalase and superoxide dismutase, and reduces the concentration of malondialdehyde. Similar mechanisms may explain the therapeutic effect of ALA in CTS, where an ischemia/reperfusion process triggers the disease.[6,27,28]

Other investigators have reported favorable results with ALA in CTS, but in these trials, ALA was given in combination with other antioxidants.[18–20] The clinical trial conducted by Pajardi *et al.*[19] reported satisfactory clinical recovery from CTS with a combination of ALA, curcumin, and vitamin B complex. Di Geronimo *et al.*[18] showed that clinical symptoms and neurophysiologic outcomes were superior in a group that took a combination of ALA and gamma-linoleic acid compared with a group that took vitamin B complex. Notarnicola *et al.*[20] verify the efficiency of shock wave therapy versus nutraceutical therapy composed of ALA, linoleic acid, quercetin, and Echinacea in CTS. Both groups showed clinical and electrodiagnostic improvement, our study differs because it is a clinical study that examines the influence of ALA as monotherapy in CTS versus placebo in patients submitted to surgical decompression of carpal tunnel, which was also blinded and controlled.

Boriani *et al.*[29] recently published the effect of ALA in CTS, they used ALA as a monotherapy after surgery for 40 days, and similar to our results, they showed good electrophysiologic and clinical response; however, we used ALA for a prolonged period of time, 4 weeks before and 12 weeks after the surgery to have better evidence of the efficacy of ALA administered for 16 weeks. The prolonged period of time allowed us to observe the recovery of the nerve since during the first 30 days after surgery, the healing progress induces an immature and intense fibrosis and the nerve does not achieve recovery.

Several studies have documented the influence of surgical treatment for CTS, but few have evaluated neurophysiologic recovery.[30–33] A follow-up study of 66 patients who underwent carpal tunnel release surgery found an improvement in distal motor latency 12 weeks after surgery, which can likely be attributed to the greater resilience to ischemia and capacity for recovery of large-caliber motor fibers compared with sensory fibers.[31] Our ALA group exhibited improvements in sensory and motor parameters, an observation that could be explained by ALA's multimodal mechanisms of antioxidant action, acting as a free radical scavenger and as a regenerator of vitamins C and E, both of which contribute to reducing oxidative stress in the peripheral nerve.[34] Our findings also suggest that ALA may hasten recovery of median nerve function, as Boston Questionnaire score had improved in the ALA group, earlier than the placebo group.

Our study does have some limitations due to its sample size and the follow-up time. We might have been able to identify further improvements in our patients if we had followed them up for 12 months, as in other studies. Furthermore, it should come to consideration that the administration of a racemic drug mixture is in reality administration of two drugs with distinct pharmacokinetic and pharmacodynamic properties. Compared with the active enantiomer, the inactive enantiomer in a racemic mixture often has different rates of absorption, metabolism, and excretion, as well as different affinities for tissue receptors. It may be an agonist or antagonist, produce adverse effects, increase efficacy, or place an undue burden on clearance mechanisms. Thus, the FDA now requires manufacturers to identify and characterize the pharmacologic properties and toxicity of each enantiomer in a racemic drug mixture before it is marketed. However, rarely the differences between stereoisomers turn out clinically significant.[35]

However, despite these limitations, great care was taken to reduce any potential effect of these confounding variables. Based on the positive results reported here, further research on the treatment efficacy of ALA is warranted.

In conclusion, we found that ALA has a neuroprotective effect, administered for 1 month before open decompression and 3 months after surgery in idiopathic CTS.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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