Original Article

Pharmacological management of mild-moderate carpal tunnel syndrome: use of Crocus sativus L. combined with alpha-lipoic acid

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Background: Carpal tunnel syndrome (CTS) is a common peripheral neuropathy that represents an important economic burden for the public health system. Some studies claim that few "functional food" or "nutraceuticals" can play a neuroprotective effect on peripheral nerves and act on neuropathic pain. The aim of the present investigation was to evaluate the role of a blend of nutraceutical substances [alpha-lipoic acid (ALA) and Crocus sativus L. (CSL)] on clinical and functional outcomes in patient affected by mild-moderate CTS.

Methods: The present investigation is a non-randomized, unblinded retrospective cohort study according the STROBE statement. We analyzed the data of 201 patients who met the inclusion and exclusion criteria. Patients were divided into 2 groups based on treatment they received (Group A: ALA 600 mg and CSL 30 mg for 90 days; Group B: ALA 600 mg for 90 days; Control Group: no treatment). The primary outcome was identified in the number of patients who refused surgery after a 1-year follow-up visit. Secondary outcomes were: pain reduction measured through visual analogue scale (VAS), patient symptoms and the functionality variation evaluated through Boston Carpal Tunnel Questionnaire (BCTQ) and side effects.

Results: In Group A we detected a statistically significant pain reduction. There were no improvements in other symptoms and function evaluated through the BCTQ between Groups A and B but we found a worsening in the Control Group patients who did not take any therapy.

Conclusions: ALA combined with CSL appears to be effective in improving the pain associated with CTS which is often the main cause of surgery. The use of the drugs analyzed seems to contain the progression of the disease compared with the Control Group. All patients awaiting surgical carpal tunnel release could be treated with neuroprotective drugs unless contraindicated.

Keywords: Carpal tunnel syndrome (CTS); alpha-lipoic acid (ALA); Crocus sativus; neuroprotection; saffron

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Introduction

Carpal tunnel syndrome (CTS) is one of the most common peripheral neuropathies and represents an important cause of lost working days, temporary disability and health care costs (1). CTS is caused by compression of the median nerve at the level of the carpus canal, this leads to ischemic damage due to alterations that occur at the level of the vasa nervorum which causes a transient irritation of the nerve fibers. When the ischemic damage is prolonged over time, due to the increase in local oxidative stress, structural damage of median nerve, such as demyelination, can occur (2,3). The typical symptoms of this syndrome include neuropathic pain, especially at night, paresthesia, dysesthesia in the innervation area of the median nerve in the early stages; in advanced stages it is possible to observe a variable motor and sensory deficit up to paralysis or anesthesia (2).

The correlation between neuropathic pain and mood disorders is known, and they both share common pathogenetic mechanisms (4,5). Furthermore, correlation between CTS and anxiety and depression has been found (6,7).

Crocus sativus L. (CSL) is flowering plant known for producing saffron, that we find on our tables every day. Ever since ancient times beneficial effects of saffron are known, and they are scientifically validated to date (8-11). CSL has peripheral and central effects as antioxidant (12-14) antidepressant (15-17) and anxiolytic (18).

Antioxidant effects of alpha-lipoic acid (ALA) have been proved and it is considered useful in treatment of neuropathic pain (2,19). Furthermore, ALA may exert neuroprotective effects in compressive neuropathies including CTS, also improving hand function (2,20,21).

The aim of the study is to clinically investigate the effect of a blend including ALA and CSL on patients suffering from mild-moderate CTS and to assess clinical and functional outcomes after 3 months. We present the following article in accordance with the STROBE reporting checklist (available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-48/rc).

Methods

Study design and aim

The current investigation is a retrospective cohort study at our Hand Surgery Department, Fondazione Policlinico Universitario Agostino Gemelli IRCCS-Presidio Columbus in Rome, since January 2017 to April 2018. The aim of the study is to evaluate the efficacy and safety of the use of neuroprotective drugs in the treatment of CTS of medium-moderate intensity. The study matched national ethics criteria, and all patients were treated and evaluated in the context of the study approved by our Institutional Review Board (Prot. n. 96/14, protocol 29390/13) (22), and was in accordance to the Helsinki agreement (as revised in 2013). All patients expressed their consent before enrollment in the study.

Institutional database and data collection

The data of patient affected by CTS referred to our unit was collected using a standardized data collection system. From these patients, we collect demographic data (age, sex, BMI), medical history, chronic therapies, smoke addiction, electromyographic data. Pain intensity was evaluated using a ten itemized point visual analogue scale (VAS). The patient symptoms and the functionality of the affected hand was evaluated through the Boston Carpal Tunnel Questionnaire (BCTQ). Patients with mild-moderate CTS undergo pharmacological or wait and see treatment and are clinically evaluated after 3 and 6 months.

Inclusion and exclusion criteria

All patients with clinical (paresthesia in the median nerve region and positive Phalen maneuvers and Tinel sign) and electromyographic diagnosis of mild-moderate CTS according with classification of Padua *et al.* (23) mono or bilateral were eligible for the study. The results have been assessed only on the dominant hand. We excluded from the study: pregnant or breastfeeding woman, patients with diabetes, patients with neuromuscular disease, moderate to severe renal dysfunction (creatinine clearance <90 mL/min), hepatopathy (MELD score >9), previous surgical carpal tunnel release, patients with diagnosis of depression, allergy or contraindication to the study drugs.

Patients assignment and groups setting

The enrolled patients were divided in two groups based on the received treatment:

- Group A: ALA 600 mg and CSL 30 mg (available in a single tablet) once a day for 90 days;
- Group B: ALA 600 mg (available in a single tablet) once a day for 90 days;
- Control Group: no drug administration.

The concomitant use of other nutraceutical substances or

Table 1 Distribution of demographic and clinical characteristics within the 3 groups

Demographics	Group A	Group B	Control Group
Number of patients	82 (40.8%)	73 (36.3%)	46 (22.9%)
Age (years)	67.1±8.9	69.3±12.6	70.1±8.9
Gender	50 F, 32 M	43 F, 30 M	29 F, 17 M
BMI	27.4±2.5	27.1±4.3	27.1±4.3
Smokers	22 (26.8%)	19 (26.0%)	12 (26.1%)
Symptom duration (months)	15.2±1.2	14.9±2.1	15.7±2.2
Comorbidities with impact on peripheral nervous system*	11 (12.4%)	8 (10.1%)	6 (13%)
Other comorbidities**	23 (26%)	19 (24%)	11 (23.9%)

Comorbidities are expressed as yes/no per each patient. *, cervical osteoarthritis, rheumatoid arthritis, cervical disc herniation; **, hypertension, hypercholesterolemia, hypothyroidism, cardiac ischemic disease, and reflux esophagitis. BMI, body mass index; F, female; M, male.

neurotrophic drugs, variations in dose administration, use of NSAIDs and splinting or other conservative treatment, were restricted.

Clinical assessment was performed after 60 and 90 days from the first administration.

ALA 600 mg once a day and CSL 30 mg once a day are the most chosen dosing regimens (8,24).

Outcomes

The primary outcome was identified in the number of patients who refused surgery after a 1-year follow-up visit. Secondary outcomes were: pain reduction measured through VAS, patient symptoms and the functionality variation evaluated through BCTQ and side effects.

Statistical analysis

Data were statistically analyzed using the Student *t*-test to compare quantitative variables. The Fishers' exact text was used for categorical variables. The significance was established for a value of $P<0.05$. Dedicated SPPS statistical calculation software (SOSS Inc., Chicago, IL, USA) was employed. Data are presented as mean and standard deviation. Only one decimal place has been reported, rounded up.

Results

Participants

Data collect from 901 patients with diagnosis of CTS were analyzed; 201 (122 F, 79 M) met the inclusion and exclusion criteria and had a good data set therefore they were enrolled in the study; 130 (64.7%) patients were right-handers. Group A included 82 patient (40.8%, 50 F, 32 M); Group B included 73 (36.3%, 43 F, 30 M) patients. Forty-six patient (22.9%, 29 F, 17 M) have not received pharmacological treatments therefore represent the Control Group.

Descriptive data

The mean age in Group A was 67.1 (±8.9) years, in Group B was 69.3 (±12.6) years while in Control Group was 70.1 (±8.9) years. The mean BMI was 27.4 (±2.5) in Group A, 26.1 (±3.0) in Group B and 27.1 (±4.3) in Control Group. In Group A 22 (26.8%) patients were smokers, in Group B 19 (26.0%) and 12 (26.1%) in the Control Group. A summary of the characteristics of the patients enrolled in the study is reported in *Table 1*. In Group A 3 patients (3.7%) left the study due to the lack of clinical improvement while Group B 8 patients (11.0%).

Outcome data and main results

- In Group A 13 patients (15.9%) refused surgical carpal tunnel release at last follow-up because of a satisfying relief of symptoms while in Group B 6 patients (8.2%) and only 3 patients (6.5%) in Control Group. The Fishers' exact was 0.14 between A and B group, 0.17 between A and C, and 1 between B and C; these results were not significative.
- In Group A the mean VAS score at t0 was 6.1 (±1.4), decreased to 3.8 (±1.3) at 60 days, to 2.6 (±1.7) at

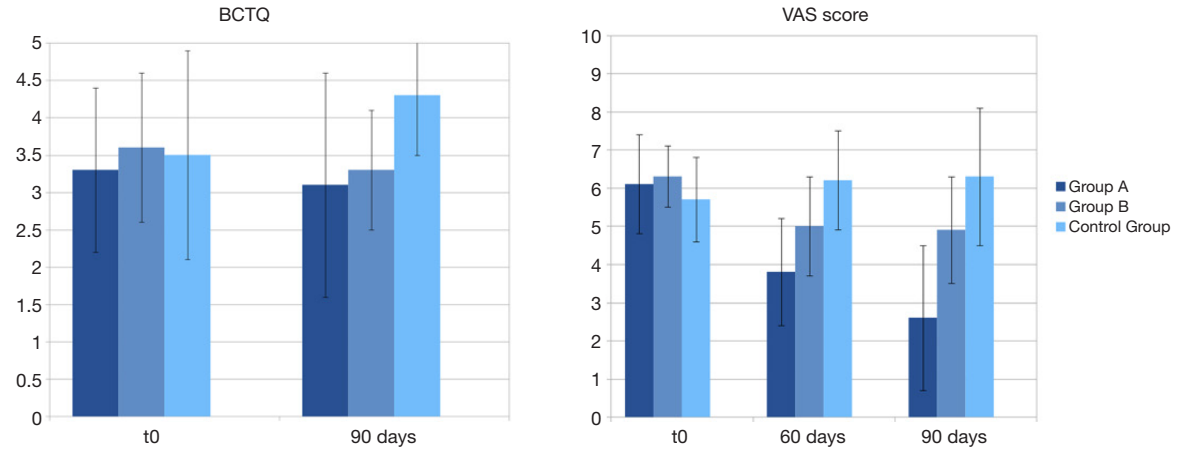

Figure 1 Change in pain and symptoms severity over the 90 days follow-up period after treatment compared to baseline (denoted by t0). Data shown represent mean ± standard deviation. In Group A exist a significative reduction of pain compared to Group B and Control Group. Symptoms severity worsens in the Control Group while remaining unchanged in Groups A and B. Group A: ALA 600 mg and CSL 30 mg; Group B: ALA 600 mg. BCTQ, Boston Carpal Tunnel Questionnaire; VAS, visual analogue scale; ALA, alpha-lipoic acid; CSL, Crocus sativus L.

90 days (P=0.03). In Group B the mean VAS score at t0 was 6.3 (±1.0), decreased to 5.0 (±1.4) at 60 days, to 4.9 (±1.4) at 90 days (P=0.08). In Control Group the mean VAS score at t0 was 5.7 (±1.1), changed to 6.2 (±1.3) at 60 days, to 6.3 (±1.8) at 90 days (P=0.07) (*Figure 1*).

- Based on the BCTQ, symptom and function are not worse after 90 days in patients of Group A, from 3.3 (±1.1) to 3.1 (±1.7) (P=0.2), and Group B, from 3.6 (±1.0) to 3.3 (±0.9) (P=0.4). In Control Group on the other hand, symptoms and function seem to get worse after 90 months, from 3.5 (±1.4) to 4.3 (±0.7) (P=0.03) according to BCTQ (*Figure 1*).
- No difference appears in the incidence of side effects between Group A and Group B (P=0.04). We found 6 case of adverse events (2.8%) in our study. Two patients (2.3%) in Group A and one patient (1.3%) in Group B reported nausea; two patients (2.6%) in Group B reported heartburn and stomach ache; one patient (1.1%) in Group A reported headache. No patients interrupted the treatment because of side effects.

Discussion

Background

According to the results in a recent systematic review, there is poor evidence of clinical improvement after non-surgical treatment of CTS: after 3 years follow-up, symptoms significantly worsen and between 23% and 89% of patients need to undergo surgical operation, however these findings should be carefully analyzed for the presence because of heterogeneity and risk of bias according the authors opinion (25). Nevertheless, different kinds of conservative treatment of CTS have been already investigated. Non-pharmacological treatment include night splinting, physical exercises and therapeutic ultrasound, and no evidence support this kinds of treatment yet (25,26). According to the pathogenesis of pain and symptoms, many drugs have been investigated (27). Corticosteroid injections have been demonstrated to improve symptoms in short term follow-ups (up to 6 weeks) (28). The use of oral corticosteroid have been investigated too, with encouraging results (29). Gabapentin has been demonstrated to improve symptoms and function on mild-moderate neuropathic pain included in CTS after 1 to 3 months follow-up (30,31). The shortness of follow-up, in respect of the possible risk of described side effects (32), cannot sufficiently justify the use of these drugs in treatment of CTS. A great interest arouses about molecules extracted from foods, improperly called “nutraceuticals”. Specific molecules are extracted from natural products and they are orally administered as dietary supplements. Since ancient times, their biologic activities are being progressively described. Compared with the past, today we can define more precisely the dose of this molecules and we able to administer them in different standardized oral forms (e.g., tablets, capsules)

(24,33). As is already done for current drugs, we can study their biological effects. Even if they are treated differently in different jurisdictions, in general "nutraceuticals" do not need of preclinical studies, unlike current drugs (34). Deriving from feeding products may have less side effect than current drugs and they are less prone to overdose effects. On the other hand, they are supposed to be less effective than drugs. These molecules are marketed in different blends and pharmaceutical forms. This makes it even more difficult to investigate their effects, but there is also a wide range of combinations possible, thus positive additive effects. ALA has antioxidant effects (13,20,35) and the benefits on relieving of post-surgical pain after CTS surgery have recently been described and demonstrated (36), improving the clinical and neurophysiologic outcomes after surgery (24). Similarly, CSL (derived from saffron) has been demonstrated to act on central and peripheral nervous system (8,37,38), improving neuropathic pain (10) and nerve function (11), but little was investigated about its role on CTS (39). Nor has there been much research into the effects of a combination of CSL and ALA.

Present investigation

Our investigation confirms the minimal clinical improvement after non-surgical treatment of CTS with nutraceuticals. In fact, no significant results have been found in terms of primary outcome (surgery refusal). The effect is not enough significant to take the place of surgery.

On the other hand, nutraceuticals can provide benefits according to the secondary outcomes. Comparing nutraceuticals administration with Control Group, a minimal benefit has been revealed, confirming that dietary improvement could play a role in symptoms relieve. However, our results could be affected by bias.

Pain rather than function is improved in patient who took CSL. Both ALA and CSL can reduce inflammation acting on converging pathways (37,38,40). We can therefore hypothesize that CSL can have an additive or even synergistic effect with ALA.

CSL may have played a role in our study improving anxiety and depression, and, consequently, at the same time improving pain (4,5).

Function (measured through BCTQ) did not significantly improve. This datum neither depends on the kind of drug nor the duration of treatment. This confirms that the effects of chronic compression of median nerve last despite drug therapy.

This is the first study that investigate the use of CSL associated with ALA in patient who suffer from mild to moderate CTS. ALA and CLS association significantly reduce the pain as evidenced by the VAS values. However, the statistical analysis did not show significant changes in the number of patients who refuse surgery, therefore the use of the drug does not convince patients not to have surgery, but it is relatively effective on symptoms.

Instead, the Control Group showed a statistically significant worsening of function compared to the other two groups. Patients of Group A were more compliant to treatment. Hence, the number of dropouts was lower in Group A compared to Group B, probably because they had take a tablet once a day, and they further have benefit from it. In our institution, the waiting list for surgery for CTS is more than 1 year long, so that our patients can benefit from this therapy before undergoing surgery. Furthermore, patients who cannot undergo surgery (because of major health problems) or who have to postpone surgery, or who do not undergo surgery for personal convictions can benefit from our non-surgical treatment (41).

Limitations

Our study had some limitations. It is a retrospective study that refers to subjective measurements (pain, functional test). A further limitation of our study is the short follow-up period, although this ensures that the symptoms and function recorded in patients in the Control Group remain unchanged over time. However, it is likely that the effects of nutraceuticals do not persist over a long period of time, nor is it certain that there is any benefit from repeated treatment.

The type of study design and the strictly selected patient group make it difficult to draw generalizations, therefore the results must be critically evaluated. More studies should be done.

Considering the effects of CSL on anxiety and depression (15-18), considering the correlation between CTS and anxiety and depression (6), it would have been useful to extend our investigation to this topic. Additionally, we did not consider a group receiving CSL alone. Further studies are needed.

Conclusions

The administration of ALA associated with CSL for 90 days appears to be relatively effective in reducing pain in

patients with mild-moderate CTS. Although improvements in BTCQ were not appreciated, it appears that the clinical progression of the disease is decelerated in the groups treated with neuroprotectors compared to the Control Group. Despite surgery still represents the gold standard of treatment, all patients awaiting surgical carpal tunnel release could be treated with neuroprotective drugs unless contraindicated.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-48/rc

Data Sharing Statement: Available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-48/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jxym.amegroups.com/article/view/10.21037/jxym-21-48/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study matched national ethics criteria, and all patients were treated and evaluated in the context of the study approved by our Institutional Review Board (Prot. n. 96/14, protocol 29390/13). All patients expressed their consent before enrollment in the study.

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