

Assessment of L-carnitine effectiveness on carpal tunnel syndrome

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Keywords

Carpal Tunnel Syndrome; Carnitine; Electrodiagnosis; Ultrasonography; Visual Analog Scale

Abstract

Background: Carpal tunnel syndrome (CTS) is the most prevalent entrapment neuropathy. Due to the results of recent studies about the protective effects of L-carnitine on nerves, this study was conducted to evaluate the effects L-carnitine on CTS improvement in terms of patient's function, electrodiagnostic study (EDX), and median nerve sonography.

Methods: In this double-blind, randomized, controlled trial, patients with CTS were selected based on the inclusion and exclusion criteria, and then, divided into two groups of placebo and L-carnitine at a dose of 500 mg twice daily for 6 weeks. They were assessed at baseline, and 4 and 6 weeks later using Boston Carpal Tunnel Questionnaire (BCTQ), median nerve conduction study (EDX), and sonography.

Results: There was no statistically significant difference between the intervention and control groups in terms of BCTQ scores, electrodiagnostic findings, and sonographic indexes. Although based on the results of the repeated measures test of the

intervention and control groups separately, there was a statistically significant difference in some electrodiagnostic criteria and BCTQ scores. These indexes improved after the intervention.

Conclusion: The effectiveness of L-carnitine on mild to moderate CTS improvement cannot be approve based on the findings of this study and more studies and systematic reviews are required in this regard.

Introduction

Carpal tunnel syndrome (CTS) is the most prevalent entrapment neuropathy; the incidence of this neuropathy varies in different geographic regions, but generally, the incidence is about 1.3 to 5%.¹⁻⁶

This syndrome may develop as a result of some pathologies? but often is idiopathic.⁵⁻⁷ Patients usually complain of hand paresthesia (often in median nerve territory), hand pain, and flick sign (nocturnal awakening due to hand pain and paresthesia).

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There are 2 groups of CTS management method, nonsurgical (such as proper splint, injection, physical agent modalities, acupuncture, laser...), and surgical intervention. Among the nonsurgical treatments, proper splint and steroid injection have been shown to be effective in the improvement of CTS signs and symptoms; there is limited evidence on other nonsurgical interventions. Surgical intervention may be the final treatment of CTS, but due to its cost and complications (such as perineural fibrosis, adhesion to anterior scar, circumferential fibrosis, and iatrogenic injury to the median nerve), it is only suggested in cases with specific indications.^{8,9} However, in patients who show indications for surgery, but do not like surgery and follow non-surgical treatments, L-carnitine is prescribed the neuroprotective effects of which have been newly confirmed.^{10,11} L-carnitine upregulates neural growth factor receptors, and thus, has neurotrophic effects.¹² In addition, it is effective in the prevention of neural cell ischemia as in vitro pretreatment.¹³

This drug decreases pain, and improves function, vibration sense, and electrodiagnostic parameters in patients with diabetic neuropathy,¹⁴ It has good effects on AIDS and chemotherapy-induced neuropathy.¹⁵ It has been shown to be effective on patients with mild to moderate CTS in terms of neurophysiological factors, function, and pain,¹⁶ but these effects have not been confirmed in postoperative patients with

severe CTS and L-carnitine may not be effective in nerve regeneration.¹⁰

In this study, we evaluated the effects of L-carnitine on improvement of CTS in terms of function, pain, and electrophysiologic and sonographic parameters of the median nerve. Thus, the main question of the study was "Can L-carnitine improve function, pain, and the electrodiagnostic and sonographic parameters of the median nerve?" Studies on this topic are limited and further research in this regard is necessary.

Materials and Methods

Each patient enrolled in this study signed an informed consent form. The present study was approved by the local Institutional Ethics Committee with the code IR.SUMS.MED.REC.1398.109 and was registered in the Iranian Registry of Clinical Trials (IRCT) with the code IRCT20200307046711N1.

The present research was a double-blind clinical trial, and the study population included people with CTS who referred to physical medicine clinics in Shiraz, Iran. In this study, during the period of 5/15/2019 to 2/3/2020, we isolated patients assumed to be suffering from CTS who had at least 2 of the symptoms of numbness, paresthesia in the territory of the median nerve in the hand, or waking up at night due to these symptoms, and selected them according to the study inclusion and exclusion criteria (Figure 1).

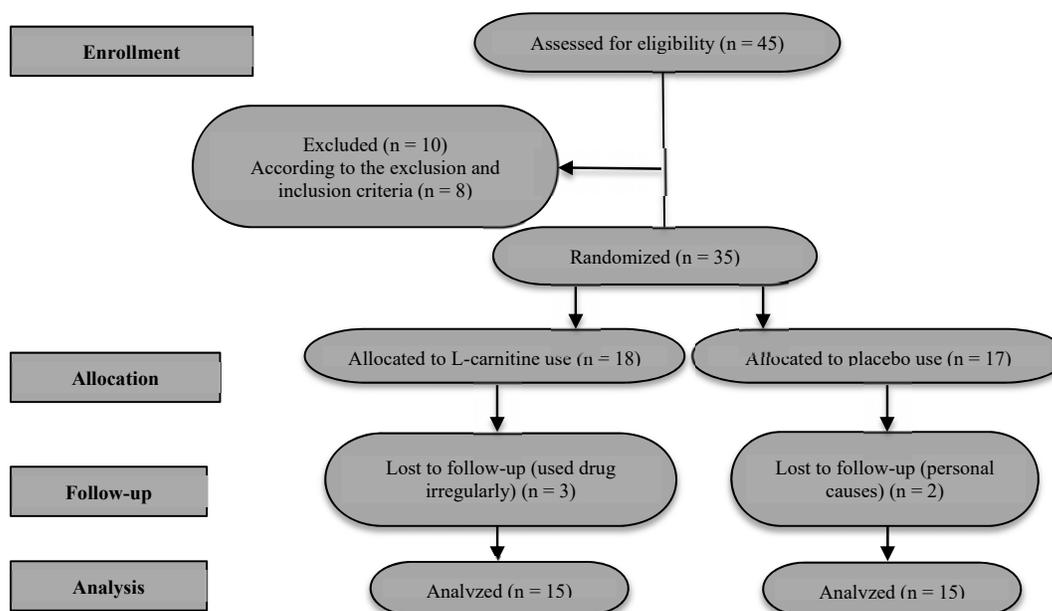


Figure 1. Consort diagram

The inclusion criteria included 18 to 60 years of age, mild to moderate CTS confirmed through electrodiagnosis, and referring to physical medicine and rehabilitation units under the supervision of Shiraz University of Medical Sciences in Shiraz.

Patients with diabetes mellitus (DM), hypothyroidism, hematologic disease, or any basic pathology that increased the risk of CTS, used drugs that caused neuropathy such as chemotherapy drugs, were pregnant or breastfeeding, or had a history of seizure, history of severe renal disease, uncontrolled hypertension, body mass index (BMI) < 18 or > 40, and severe CTS were excluded from this study.

Using block randomization method, individuals were divided into intervention and control groups. Thus, considering the number of treatment groups (2 groups), we considered 4 size blocks. We indicated the first group with the letter A and the second group with the letter B, and using random allocation software, a sequence of different permutations of 4 blocks (AA, BB, ...) was produced, which determined the order of patients in groups. In this double-blind study, patients and the person performing EDX were completely unaware of how individuals were assigned to treatment groups. After EDX and confirmation of CTS, patients were referred to a pharmacy, where they received placebo or L-carnitine based on the previously mentioned randomization method.

EDX was performed to diagnose CTS and rule out other neuropathies. In total, 35 people participated in the study; 2 people withdrew from the study, and 3 people who did not take L-carnitine regularly were excluded from the study.

After the EDX, we randomly classified the patients into 2 groups: one placebo group (starch-containing capsules with cans similar to L-carnitine), and the L-carnitine (Karen company, 500 mg twice daily) group. Both groups were given standard wristbands. The Boston Carpal Tunnel Questionnaire (BCTQ) and visual analogue scale (VAS) were completed for each person at the beginning of the study (before giving L-carnitine), and 4 and 6 weeks after starting L-carnitine, and EDX and sonography were performed. We compared information and data of the control and intervention groups before and after the intervention.

Evaluations in participants

Electrophysiological evaluation: Nerve conduction and electromyography (EMG) testing was performed using Natus electromyography

device with felt electrode lead (two felts with a diameter of 6 mm at a distance of 20 mm from each other), skin temperature was at least 31 °C during EMG testing and 25-28 °C at room temperature. Moreover, median CMAP latency, median SNAP latency, median CNAP latency, and median SNAP NCV across the wrist were measured according to the standard.¹⁷

We used the Bland classification system to exclude individuals with severe CTS.¹⁸

Evaluating symptoms severity and hand function: The BCTQ was used in the present study. The BCTQ consists of 18 questions, 11 are related to pain intensity, weakness, numbness, difficulty of grasping, and 7 are related to function. Each question has a maximum score of 5, with a score of 1 indicating a normal state and a score of 5 indicating the most severe state. The mean score obtained from these cases ultimately determines the severity of symptoms and the degree of dysfunction. The validity and reliability of this questionnaire have been confirmed in Iran.¹⁹ The severity of pain was evaluated using a VAS.

Sonography: We measured cross-sectional area (CSA) using a Philips HD5 ultrasonic transducer (5-12 MHz) device at the entrance of the carpal tunnel (at the periphery of the pisiform) before, and 4 weeks and 6 weeks after the intervention. In previous studies, the normal diameter of the median nerve at the entrance of the carpal tunnel was estimated to be approximately 10 mm².^{20,21}

Results

Age and gender: This study was conducted to assess the efficacy of L-carnitine on CTS in 30 patients of 18 to 60 years of age whose CTS was confirmed through electrodiagnosis and their clinical signs. The mean age of the participants in the intervention and placebo group was 40.4 years and 44.93 years, respectively. The results of the Kolmogorov-Smirnov test illustrate that the patients' age data follow the normal distribution ($P = 0.824$). The results of the Student's t-test confirmed that there was no statistically significant difference between the two groups in terms of mean age ($P = 0.102$).

Sonography: The Mann-Whitney U test results showed that there was no statistically significant difference between the intervention and placebo groups in terms of median nerve cross-section area in an ultrasound/sonography before L-carnitine administration ($P = 0.884$), and the two groups were the same (Table 1).

Table 1. Mean and standard deviation of cross-sectional area (CSA) in the two groups studied in terms of mm²

Studied groups	Intervention (L-Carnitine) (mean ± SD)	Control (placebo) (mean ± SD)	P
CSA 1 (Before prescribing placebo/L-carnitine)	0.185 ± 0.188	0.159 ± 0.054	0.884
CSA 2 (after 4 weeks)	0.132 ± 0.019	0.153 ± 0.040	0.184
CSA 3 (after 6 weeks)	0.131 ± 0.019	0.145 ± 0.031	0.260

CSA: cross-sectional area; SD: Standard deviation

Moreover, there was no statistically significant difference between the two groups in terms of median nerve cross-section 4 weeks after ($P = 0.184$) and 6 weeks after the administration of L-carnitine ($P = 0.260$) (CSA), (Table-1).

Electrodiagnostic Findings

Median SNAP latency of the second finger:

According to the results of the Kolmogorov-Smirnov test, median SNAP latency data of the second finger before treatment ($P = 0.600$), 4 weeks after treatment ($P = 0.730$), and 6 weeks after treatment ($P = 0.830$) follow a normal distribution. The results of the Student's t-test showed no statistically significant difference between the case and control groups in the median SNAP latency of the second finger before L-carnitine treatment ($P = 0.740$). Furthermore, the results of the Student's t-test showed no statistically significant difference between the intervention and control groups in terms of median SNAP latency of the second finger 4 weeks ($P = 0.926$) and 6 weeks ($P = 0.402$) after L-carnitine administration.

Median SNAP latency of the third finger: Data related to median SNAP latency achieved by the third finger before ($P = 0.730$), 4 weeks after ($P = 0.990$), and 6 weeks after L-carnitine administration ($P = 0.830$) follow the normal distribution. The above comparisons were performed using the Student's t-test.

The results of the Student's t-test revealed that there was no statistically significant difference in the median SNAP latency of the third finger before L-carnitine administration between the case and control groups ($P = 0.323$). Additionally, the results of the Student's t-test showed no statistically significant difference in median SNAP latency of the third finger between the intervention and control groups 4 weeks ($P = 0.401$) and 6 weeks ($P = 0.702$) after L-carnitine administration.

Median sensory nerve speed in the wrist: The results of the Mann-Whitney U test confirmed that there was no significant difference in median sensory nerve speed in the wrist ($P = 0.918$) before L-carnitine administration between the intervention and placebo groups and the two groups were the same.

Furthermore, no statistically significant difference was observed between the two groups in terms of sensory speed of the median nerve in the wrist 4 ($P = 0.817$) and 6 weeks after L-carnitine administration ($P = 0.768$).

Median CMAP latency: Median CMAP latency data followed normal distribution before L-carnitine administration ($P = 0.630$), 4 weeks after administration ($P = 0.780$), and 6 weeks after administration ($P = 0.920$). As the results of Student's t-test showed, no statistically significant difference was observed in the median CMAP latency before L-carnitine administration between the intervention and control groups ($P = 0.965$). The results of Student's t-test indicated no statistically significant difference in median CMAP latency between the intervention and control groups 4 weeks ($P = 0.766$) and 6 weeks ($P = 0.591$) after L-carnitine administration.

Median CNAP latency: Student's t-test revealed that there was no statistically significant difference in median CNAP latency before L-carnitine administration between the intervention and control groups ($P = 0.458$). Additionally, the results of Student's t-test showed no statistically significant difference in median CNAP latency between the intervention and control groups 4 weeks ($P = 0.878$) and 6 weeks ($P = 0.965$) after L-carnitine administration. Table 2 shows the above results.

Median CMAP amplitude: According to the Kolmogorov-Smirnov test results, median CMAP amplitude data followed normal distribution before L-carnitine administration ($P = 0.632$), and 4 weeks ($P = 0.788$) and 6 weeks after L-carnitine administration ($P = 0.924$). The Student's t-test showed no statistical significance difference in median CMAP amplitude before L-carnitine administration between the control and intervention groups ($P = 0.623$).

Furthermore, the results of Student's t-test showed no statistically significant difference in median CMAP amplitude between the intervention and control groups 4 weeks ($P = 0.786$) and 6 weeks ($P = 0.562$) after L-carnitine administration (Table 2).

Table 2. Mean and standard deviation of electrodiagnostic findings in the two studied groups

Studied groups	Intervention (L-Carnitine) (mean ± SD)	Control (placebo) (mean ± SD)	P
Mean and standard deviation of median SNAP latency of the second finger in terms of millisecond			
Median SNAP* latency of the second finger (before treatment with L-carnitine/placebo)	4.06 ± 0.46	4.02 ± 0.48	0.740
Median SNAP latency of the second finger (after 4 weeks)	4.02 ± 0.45	4.04 ± 0.48	0.926
Median SNAP latency of the second finger (after 6 weeks)	4.02 ± 0.47	3.89 ± 0.34	0.402
Mean and standard deviation of Median SNAP latency of the third finger in terms of millisecond			
Median SNAP latency of the third finger (before treatment with L-carnitine/placebo)	4.21 ± 0.41	4.05 ± 0.43	0.323
Median SNAP latency of the third finger (after 4 weeks)	4.13 ± 0.38	3.99 ± 0.48	0.401
Median SNAP latency of the third finger (after 6 weeks)	3.96 ± 0.38	4.02 ± 0.45	0.702
Mean and standard deviation of the sensory speed of the median nerve in the wrist in terms of meters per second			
Median speed criterion (before treatment with L-carnitine/placebo)	36.80 ± 4.86	37.26 ± 5.13	0.918
Median speed criterion (after 4 weeks)	37.91 ± 3.32	38.20 ± 4.45	0.817
Civic Speed Criterion (after 6 weeks of treatment with L-carnitine)	39.12 ± 6.23	39.10 ± 5.58	0.768
Mean and standard deviation of median CMAP latency in terms of millisecond			
Median CMAP** latency (before treatment with L-carnitine/placebo)	4.21 ± 0.33	4.20 ± 0.74	0.965
Median CMAP latency (after 4 weeks)	4.05 ± 0.48	4.11 ± 0.64	0.766
Median CMAP latency (after 6 weeks)	3.93 ± 0.47	4.04 ± 0.70	0.591
Mean and standard deviation of median CNAP latency in terms of millisecond			
Median CNAP*** latency (before treatment with L-carnitine/placebo)	2.78 ± 0.32	2.67 ± 0.44	0.458
Median CNAP latency (after 4 weeks)	2.60 ± 0.37	2.62 ± 0.44	0.878
Median CNAP latency (after 6 weeks)	2.62 ± 0.34	2.62 ± 0.46	0.965
Mean and standard deviation of median CMAP amplitude in terms of MV			
Median CMAP amplitude (before treatment with L-carnitine/placebo)	6.80 ± 2.92	6.38 ± 1.47	0.623
Median CMAP amplitude (after 4 weeks)	6.99 ± 2.55	7.22 ± 2.07	0.786
Median CMAP amplitude (after 6 weeks)	6.74 ± 2.46	7.26 ± 2.37	0.562

*Sensory nerve action potential, **Compound muscle action potential, ***Compound nerve action potential
SD: Standard deviation

BCTQ: According to the results of Student's t-test, there was no statistically significant difference between the intervention and control groups in terms of mean scores of BCTQ (examining symptom severity and functional weakness) before the intervention ($P = 0.539$), 4 weeks after the intervention ($P = 0.955$), and 6 weeks after the intervention with L-carnitine (Table 3).

VAS: According to the results of Mann-Whitney U test, pain showed no statistically

significant difference at 4 weeks ($P = 0.539$) and 6 weeks ($P = 0.389$) after the intervention between the two groups. Table 4 explains the above results (Table 4).

Discussion

This study aimed to assess the efficacy of L-carnitine in CTS in 30 patients of 18 to 60 years of age, whose CTS was confirmed through electrodiagnosis and clinical signs.

Table 3. Mean and standard deviation of Boston Carpal Tunnel Questionnaire (BCTQ) scores in the two studied groups

Studied groups	Intervention (L-Carnitine) (mean ± SD)	Control (placebo) (mean ± SD)	P
BCTQ (Before treatment with L-carnitine/placebo)	38.93 ± 10.05	36.13 ± 14.23	0.539
BCTQ (after 4 weeks)	31.53 ± 9.45	33.33 ± 12.48	0.660
BCTQ (after 6 weeks)	31.20 ± 9.65	31.00 ± 9.75	0.955

SD: Standard deviation; BCTQ: Boston Carpal Tunnel Questionnaire

Table 4. Mean and standard deviation of visual analogue scale (VAS) pain standard scores in the two groups

Studied groups	Intervention (L-Carnitine) (mean ± SD)	Control (placebo) (mean ± SD)	P
VAS/pain criterion (Before treatment with L-carnitine / placebo)	7.98 ± 1.17	6.64 ± 1.28	0.006
VAS /Visual Analogue Scale pain criterion (after 4 weeks)	5.57 ± 1.63	5.21 ± 1.45	0.539
VAS/pain criterion (after 6 weeks)	4.97 ± 2.47	4.83 ± 1.62	0.389

SD: Standard deviation; VAS: Visual analogue scale

The results showed no statistically significant difference between the two groups of control and intervention with L-carnitine in terms of gender ($P = 0.224$) and mean age ($P = 0.102$). Additionally, the intervention and control groups were the same in terms of all studied variables.

In general, there was no significant difference between the control and intervention groups in terms of the effectiveness of L-carnitine on CTS in this study. However, each group experienced relative improvement individually in statistical studies during follow-up 4 and 6 weeks after the intervention, which may be due to the standard treatment of CTS in each group. Cruccu et al.¹⁶ conducted a similar study and confirmed the efficacy of L-carnitine on CTS. This study and the current study defer in terms of several cases. Their study had no control group and has examined the intervention group over time. Although the standard treatment of carpal tunnel syndrome was not discussed in their study, in the present study, relative improvement was seen in the intervention group during the time. Cruccu et al. administered L-carnitine, first, intramuscularly for several days, and then, 500 mg twice daily. Although the intramuscular dose of L-carnitine was not given in this study, its oral dose is similar to the mentioned study;¹⁶ no researcher has conducted a study on the difference between these two methods of administering L-carnitine. In the study by Cruccu et al., L-carnitine administration lasted 4 months, and follow-ups were performed on days 0, 10, 60, and 110. This period was 6 weeks in the present study, and follow-ups were performed at weeks 0, 4, and 6. The dose of L-carnitine utilized for neuropathy in various papers was 500 mg to 3 g, which was injected intramuscularly for 10 to 15 days before the start of oral L-carnitine in some cases.^{10,22-24}

As the results of sonography in this study show, there was no statistically significant difference in the CSA of the median nerve (CSA) between the intervention and control groups 4 weeks ($P = 0.184$) and 6 weeks after the intervention ($P = 0.260$). A

decrease was observed in the cross-section area of the median nerve (CSA) after the intervention with L-carnitine, but this decrease was not statistically significant. Various studies have described environmental conditions and appropriate criteria for sonographic evaluation of the median nerve, but there is not much consensus in this regard.^{5,18,25-28} No comparative study has been conducted concerning the efficacy of L-carnitine on median nerve ultrasound criteria in CTS.

Di et al. conducted a systematic study on L-carnitine in painful peripheral neuropathies and concluded that L-carnitine was efficient in toxic neuropathies caused by antiviral drugs, chemotherapy-induced neuropathy, and diabetic neuropathy, and EDX showed a significant improvement.²² Neuropathies caused by chemotherapy or diabetes are normally axonal, and neuropathy related to CTS is initially demyelinating. It is not clear whether this point creates a bias in the comparison of these two studies or not, but even the effect of L-carnitine has been different on chemotherapy with different drugs. Rolim et al. conducted a systematic study to investigate the effect of L-carnitine in the treatment of peripheral neuropathy due to diabetes.²³ They observed no effect of L-carnitine on diabetic neuropathy, and more scientific evidence is required in this regard because there is inadequate evidence and the available evidence has low precision.²³

There are many studies on treatment with L-carnitine, and Li et al. conducted a study on the effects of L-carnitine and methylcobalamin on diabetic neuropathy and concluded that the Effects of L-carnitine on diabetic neuropathy are approximately similar, and generally, evaluated the effects of L-carnitine for 24 weeks in patients with diabetic neuropathy as positive because L-carnitine improved clinical signs and physiological parameters in neuropathy.²⁴

In general, L-carnitine was prescribed at a dose of 1 to 3 grams for 6 to 24 months. The effect of L-carnitine on chemotherapy-induced

neurotherapy, and diabetic neuropathy was investigated in these studies. In most studies, the effectiveness of L-carnitine was confirmed.^{22,24} However, its effectiveness has not been sufficiently and completely supported in some systematic studies.²³ In general, this case requires more accurate evidence. The duration of L-carnitine administration was longer in these studies than in the present study.

Curran et al. conducted a study to evaluate the effect of L-carnitine on nerve regeneration in 20 patients suffering from severe CTS after surgery and releasing of the flexor retinaculum. No significant difference was observed between L-carnitine and placebo groups, and both groups improved in the course of the study after 12 months of taking L-carnitine at a dose of 3 g per day. Thus, this study did not support the effect of L-carnitine on nerve regeneration and functional improvement in patients suffering from CTS.¹⁰ The results of this study were consistent with that of the present study, but in they studied severe CTS cases after surgery. Thus, their findings may not be generalizable to the mild and moderate cases studied in the present study.

As the findings of our study show, the mean scores of the BCTQ (examining symptom severity and functional weakness) showed no statistically significant change 4 weeks and 6 weeks after L-carnitine intervention, which is in agreement with the findings of some previous studies. However, it is inconsistent with the findings of some other studies. For example, Cruccu et al. conducted a study in 2017 to assess the effects of L-carnitine on pain and function in 120 hands of 82 patients with mild to moderate CTS with a 4-month follow-up. Patients were evaluated at the beginning and 10, 60, and 120 days after treatment with 500 mg L-carnitine twice a day (BID). BCTQ and Neuropathic Pain Symptom Inventory (NPSI) were used to evaluate the median nerve in all patients. The mean score of the BCTQ differed significantly ($P < 0.001$). There was a significant reduction in the NPSI score of patients.¹⁶ This inconsistency may be due to the living conditions, examination conditions, and definitions of pain in patients. According to the results of our study, the two methods of ultrasound and electrodiagnostic testing showed no statistically significant difference 4 and 6 weeks after the intervention in terms of the studied indices compared to before the intervention.

It may be necessary to check the blood level of

L-carnitine when L-carnitine is administered orally. The amount of L-carnitine absorption is different depending on the number of intestinal bacteria. Consequently, a more accurate dose of L-carnitine can be given to the patient. Regrettably, patients' blood L-carnitine levels were not checked due to specific limitations in this study. We observed one case of paresthesia in the lower organs and one case of polyuria during treatment with L-carnitine.

Conclusion

As the findings of this study show, in general, L-carnitine significantly affects the improvement of mild to moderate CTS. We cannot confirm the effectiveness of this drug in treating CTS, and further studies and broader systematic studies are necessary.

It is recommended in future studies that a longer course of medication and follow-up be considered for patients if possible. If possible, the blood level of L-carnitine should be checked, and a control group should be employed for comparison. **Limitations:** We could possibly have concluded more accurately in this study by increasing the sample size and follow-up time. Due to time constraints, the duration of L-carnitine consumption by patients and follow-up time were short. Moreover, the sample size was not large.

The subjects were mostly women, and there were few men. This drug may have a different effect on men.

Conflict of Interests

The authors declare no conflict of interest in this study.

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Patients signed an informed consent form, and the required information was presented orally to them. The subjects could leave the study whenever they wanted. Patients with severe CTS were excluded from the study because they needed faster treatment.

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