

Systematic Review of the Benefit of Acetyl-L-Carnitine in Diabetic Neuropathy

Rizaldy Pinzon, Fransiscus Buwana

Neurology Department, Duta Wacana Christian University School of Medicine

Abstract

Diabetic neuropathy is the most common form of neuropathy pain condition. The available treatment mainly focus in symptom control. Acetyl-L-carnitine (ALC) has shown a neuroprotective effect in patients with peripheral neuropathies of different etiologies. The preclinical studies demonstrated a central anti-nociceptive action, both in neuropathic and nociceptive pain models. The present review aims to provide the knowledge on the efficacy of ALC in patients with painful diabetic neuropathy. Consistent with the PRISMA statement, authors searched PubMed, Embase and the Cochrane Database of Systematic Reviews for relevant papers, including those issued before 2019. Two authors independently selected studies for inclusion and data extraction: only trials including patients with a diagnosis of diabetic neuropathy and involving at least 10 patients were considered for the purposes of this review. The selected studies showed beneficial effects of ALC in symptoms reported and on nerve conduction parameters and nerve fiber regeneration. ALC has a good safety profile. These data indicate that ALC provides an effective and safe treatment in patients with painful diabetic neuropathy. We recommend further trials to assess the optimal dose and duration of the therapeutic effect (also after treatment withdrawal).

Key words: Acetyl-L-carnitine, diabetic neuropathy, pain, systematic review

INTRODUCTION

Several treatment options for painful diabetic neuropathy are available, including pharmacological, non-pharmacological, and alternative options.¹⁻³ Patients suffering from severe and disabling symptoms may require treatments like pregabalin, duloxetine, or gabapentin initially until the symptoms are under control.^{2,4} These medications can symptomatically relieve in some cases; however, they do not address the underlying cause. Other options such as The acetyl-L-carnitine (ALC) do not only target the symptoms, but also improve nerve health and contribute to nerve regeneration.²

The acetyl-L-carnitine (ALC) is produced by the human brain, liver and kidney, represents one of such recent therapeutic approaches. This molecule is an acetyl-group donor and plays an important role on mitochondrial energy homeostasis and detoxification.^{5,6}

The ALC will strengthening the actions of Nerve Growth Factor (NGF) actions and promoting peripheral nerve regeneration. The ALC revealed a neuroprotective function in animal models of diabetic neuropathy.⁶ Several

experimental models of neuropathic pain documented the antinociceptive effect of ALC.^{6,7}

There is no systematic review of ALC that focused only in painful diabetic neuropathy yet. This systematic review aim to provide the actual knowledge, based on the evidence, of ALC efficacy compared to placebo in the treatment of pain in patients with diabetic neuropathy.

METHOD

We searched PubMed, Embase and the Cochrane Database of Systematic Reviews for relevant papers, considering publications issued between 2010 and 2019. The following search terms were used: “acetyl-L-carnitine”, “diabetes neuropathic pain”, and “neuropathy”. Full-length, original articles were included, limiting the search to English-language publications. The review process was carried out by two reviewers: only publications independently approved by the two authors were taken into account The following inclusion criteria were considered: trials including patients with a diagnosis of diabetic neuropathic pain, and a minimum sample size of 10 patients. A revision of the selected clinical trials was carried out, to provide the level of evidence.

Table 1. Characteristic of the trials

Author (year)	Design	Subjects	Dose
Sima (2005)	Randomized controlled Trial	1257 patients with diabetic neuropathy	500 or 1000 mg ALC
De Grendis (2002)	Randomized controlled Trial	333 patients with diabetic neuropathy	2000 mg
Li (2016)	Randomized controlled Trial	232 patients with diabetic neuropathy	500 mg

Table 2. Validity assessment of the trials

Author (year)	Randomization	Blind assessment	Follow up	Intent to treat analysis
Sima (2005)	Yes	Yes	13 months (complete)	Yes
De Grendis (2002)	Yes	Yes	12 months (complete)	Yes
Li (2016)	Yes	Yes	6 months (complete)	Unclear

Table 3. The finding of the trials

Author (year)	Outcome measurement	Finding
Sima (2005)	VAS and Nerve Conduction Velocity	VAS reduction -25 ± 28 mm for 500 mg and VAS reduction -21 ± 34 mm for 1000 mg
De Grendis (2002)	VAS and nerve Conduction Velocity	VAS reduction -39% compared to the baseline and NCS improvement $\pm 5,7$ m/sec
Li (2016)	NCS and Neuropathy Symptom Score	NCS improvement $5,03\pm 0,78$ msec and neuropathy symptom score improvement $3,01\pm 4,25$

RESULTS

We found three RCT that meet inclusion criteria. The 3 RCT compared ALC versus control with diabetic peripheral neuropathy. The studies measured the pain improvement using VAS. The three studies have a good quality based on the randomization, blind outcome measurement, long follow up period, and intent-to treat based analysis (Table 1 and 2)

Sima, et al performed two RCTs with the same design. ALC was administered at two doses (500 or 1,000 mg) three times a day (t.i.d.) for 1 year. Patients treated with 1,000 mg ALC t.i.d. showed significant improvement in 6 months and 1 year.⁹

Further analysis showed that type 2 diabetes, adequate drug compliance, and HbA1c $<8.5\%$ were associated to the greatest benefit in pain reduction. Pain relief was linked to improvements in clinical symptom scores. No significant differences in nerve conduction study data and in the incidence of adverse events between the two groups of patients were observed.⁹

Another RCT by De Grandis, et al use 1,000 mg/ day of ALC were administered intramuscularly for 10 days; the dosage was then raised to 2,000 mg/day, administered orally, until the end of the study (355 days).¹⁰ After 12 months of treatment, a significant reduction in the mean VAS scores for pain was observed in patients treated with ALC, compared with the placebo group. A significant improvement in nerve conduction study parameters was also found in treated patients. No serious adverse events were reported.

A multicenter, double-blind RCT assessed the efficacy and safety of ALC in diabetic peripheral neuropathy com-

pared with methylcobalamin.¹¹ The study was performed in 232 patients. The sample were randomized to receive oral ALC 500 mg t.i. d. or methylcobalamin 500 mg t.i.d. for 24 weeks. At the end of the treatment period, patients from both groups showed significant reductions in both the neuropathy symptom score and neuropathy disability score, with no meaningful difference between the two groups. Neurophysiological parameters were also improved in both groups.¹¹ Table 3 showed that the 3 trials consistently found that the ALC is beneficial in reducing pain, symptom improvement, and nerve conduction velocity improvement.

DISCUSSION

Our systematic review found that ALC is beneficial for patients with diabetic neuropathy. Based on the preclinical and clinical studies, ALC can be considered effective both an etiological and symptomatic treatment in patients with peripheral neuropathy. The ALC also has good safety profile. The ALC operates via several mechanisms, inducing regeneration of injured nerve fibers, reducing oxidative stress, promoting DNA synthesis in mitochondria, and increasing NGF concentrations in neurons, thus promoting neurite extension.^{12,13}

A lack of carnitine reduces energy synthesis by impairing fatty acid degradation. This condition was reported in association with diabetes and its complications.¹² The ALC showed analgesic properties, by relieving acute and in chronic pain. Several works, describing different neuropathic pain models, confirmed the antinociceptive effect of ALC. Such an effect results from different mechanisms, including the activation of muscarinic

cholinergic receptors, and the increased expression of mGlu2 receptors in dorsal root ganglia neurons, by means of an acetylation mechanism involving transcription factors of the nuclear factor (NF)-kappaB family.^{13,14} Noteworthy, the analgesic effect of ALC exceeds by several days or weeks the end of treatment, in models of chronic inflammatory and neuropathic pain. This enforces the role of ALC as an analgesic drug and supports the role of the epigenetic mechanisms in the treatment of chronic pain.¹⁴

This review has some limitations. This review found some heterogeneity among the study. The review only include papers that published in English. Future trials in patients with painful peripheral neuropathy of different etiology are needed.

CONCLUSION

This review showed that ALC is an effective and safe treatment in painful diabetic neuropathy. Future studies aiming to assess the duration of the therapeutic efficacy in larger populations, possibly with longer follow-up periods, are required.

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Authors Contribution:

RP - Concept and design of the study, manuscript preparation, statistically analyzed and interpreted, critical revision of the manuscript.

FB - Concept and design of the Study, collected data, preparing first draft of manuscript, critical revision of manuscript and review of the study.

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