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REVIEW
THERAPY OF ENDOCRINE DISEASE

A systematic review and meta-analysis of α-lipoic acid in the treatment of diabetic peripheral neuropathy

Tingting Han, Jiefei Bai, Wei Liu and Yaomin Hu

Department of Endocrinology, Renji Hospital, Shanghai Jiaotong University, 200127 Shanghai, China

(Correspondence should be addressed to Y Hu; Email: amin1031@hotmail.com)

Abstract

Objective: To evaluate the effects and safety of 300–600 mg α-lipoic acid (ALA) given i.v. for diabetic peripheral neuropathy (DPN).

Methods: We searched the databases of Medline, Embase, and Cochrane central register of Controlled Trials and Chinese biological medicine for clinical trials of ALA in the treatment of DPN. Data were extracted to examine methodological quality and describe characteristics of studies. The primary outcomes were efficacy, median motor nerve conduction velocity (MNCV), median sensory nerve conduction velocity (SNCV), peroneal MNCV, and peroneal SNCV. Secondary outcomes were adverse events.

Results: Fifteen randomized controlled trials met the inclusion criteria. The treatment group involved the administration of ALA 300–600 mg i.v. per day. And the control group used the same interventions except for ALA. Compared with the control group, nerve conduction velocities increased significantly in the treatment group. The weighted mean differences in nerve conduction velocities were 4.63 (95% confidence interval 3.58–5.67) for median MNCV, 3.17 (1.75–4.59) for median SNCV, 4.25 (2.78–5.72) for peroneal MNCV, and 3.65 (1.50–5.80) for peroneal SNCV in favor of the treatment group. The odds ratio in terms of efficacy was 4.03 (2.73–5.94) for ALA. Furthermore, no serious adverse events were observed during the treatment period.

Conclusions: The results of this meta-analysis provide evidence that treatment with ALA (300–600 mg/day i.v. for 2–4 weeks) is safe and that the treatment can significantly improve both nerve conduction velocity and positive neuropathic symptoms. However, the evidence may not be strong because most of the studies included in this meta-analysis have poor methodological quality.

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Introduction

A large number of studies suggest that oxidative stress plays an important role on the pathogenic mechanism of diabetic peripheral neuropathy (DPN) (1, 2). The mechanism of the improvement in neuropathic symptoms with α-lipoic acid (ALA) may be related to an improvement in nerve blood flow mediated by the antioxidant action (3, 4, 5, 6, 7). ALA can also reduce levels of interleukin 6 and plasminogen activator 1 in plasma, suggesting that it may improve endothelial dysfunction through anti-inflammatory and anti-thrombotic mechanisms (8). It is notable that ALA may improve nitric oxide-mediated endothelium-dependent vasodilation in diabetic patients (9). Consequently, ALA has shown that it could improve diabetic neuropathy.

By assessing quantitative tables such as total symptom score (TSS), neuropathy impairment score (NIS), and NIS of the lower limbs (NIS-LL), a previous meta-analysis including four trials (Alpha-Lipoic Acid in Diabetic Neuropathy (ALADIN), ALADIN β, Symptomatic Diabetic Neuropathy (SYDNEY), and Neurological Assessment of Thioctic Acid in Neuropathy (NATHAN) α) has demonstrated that ALA given 600 mg i.v. per day over 3 weeks improved the chief symptoms of diabetic polyneuropathy. And also the adverse events did not differ between the ALA group and placebo group (10). In recent years, many studies investigating the effect of ALA on DPN have been conducted. Efficacy was defined as amelioration of symptoms, tendon reflex, and nerve conduction velocities (NCVs) in these studies. Objective laboratory measures such as NCVs were used in most of the trials. Thus, by estimating the above-defined efficacy and NCVs, we did a systematic review to further evaluate the effects and safety of ALA in patients with DPN.

Materials and methods

Sources

Using databases of Medline from 1966 to December 2011, Embase from 1980 to December 2011, the fourth

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quarter 2011 Cochrane central register of controlled trials, and Chinese Biological Medicine from 1978 to December 2011 without language limitation, we conducted a comprehensive and systematic search of the published literature for trials of ALA in the treatment of DPN. The key words used in this search were ALA or thioctic acid and DPN or diabetic neuropathies.

Selection criteria

We included randomized controlled trials (RCTs) that investigated ALA effects for patients of DPN and excluded nonrandomized trials and clinical observations. The treatment group involved the administration of ALA given 300–600 mg i.v. per day. The control group used the same interventions except for ALA.

Quality assessment

We used a three-item, 1–5 quality scale to score each report that met the inclusion criteria (11). Use of concealment and intention-to-treat analysis were also assessed. Two of the three reviewers made quality assessment, and their disputes were settled by consensus.

Data extraction

Study design data including design synopsis, daily dose of ALA and duration of treatment were abstracted, along with patient baseline characteristics. End point outcomes were also abstracted. These data were independently extracted by two reviewers.

Outcome

The primary end point outcomes were efficacy, median motor nerve conduction velocity (MNCV), median sensory nerve conduction velocity (SNCV), peroneal MNCV, and peroneal SNCV. We defined efficacy as improvement of symptoms, tendon reflex, and NCVs. Secondary outcomes were adverse events.

Statistical analysis

We combined the results and expressed them as odds ratio (OR) or weighted mean difference (WMD) with 95% confidence intervals (95% CIs), using a fixed effect (FE) or randomized effect (RE) model, for the studies with sufficient data. And homogeneity was assessed with the I^2 statistic and χ^2 test. The above statistical calculations were performed on Revman Manager 5.0 Software (Copenhagen, Denmark) for meta-analysis. Sensitivity analysis was applied to explore the influence on outcomes through changing effect model or excluding studies with abnormal results. Publication bias was examined by using a funnel plot.

Results

Description of the studies

We screened 163 citations for eligibility and retrieved 18 full-text articles published in Chinese and six in English, eight of which used TSS or NIS to evaluate the effectiveness. Though another study measured nerve conduction velocities, its outcomes of sural SNCV and tibial MNCV were based on given ALA i.v. for 5 days followed by long-term oral supplement (12). All these above studies were excluded. Finally, 15 articles that met the inclusion criteria were included in our meta-analysis (13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27). Table 1 shows the characteristics and methodological quality of the included studies.

Table 1 Characteristics and methodological quality of included studies.

Trial	Number (T/C)	Age (mean) T/C	Intervention	Control	ALA dose (mg/day)	Duration (days)	Quality
Zhao (2008)	75 (39/36)	54.5/55.3	A+M	M	600	21	C
Zou *et al.* (2008)	60 (30/30)	65.0/66.0	A+P+M	P+M	600	14	C
Huang *et al.* (2008)	60 (30/30)	62.3/63.4	A+P	P	600	14	C
Zhang *et al.* (2009)	60 (30/30)	58.8/59.0	A+M	M	600	21	C
Suo & Zhang (2009)	64 (32/32)	62.3/63.1	A+M	M	600	14	C
Li & Xu (2008)	90 (45/45)	43.9/47.6	A+G	G	600	14	C
Wang (2009)	80 (40/40)	55.9/57.6	A+M	M	600	28	C
Wu *et al.* (2008)	86 (46/40)	60.0/61.0	A+P	P	450	14	C
Fu (2008)	67 (33/34)	50.0/54.0	A+M	M	300	21	C
Li (2008)	78 (39/39)	58.6/57.1	A+M	M	600	21	C
Xia *et al.* (2008)	74 (38/36)	61.7/62.0	A+V	V	600	21	C
Chen *et al.* (2008)	38 (19/19)	51.8/53.7	A+P	P	600	14	C
Lu (2009)	50 (27/23)	56.1/56.2	A+L	L	600	21	C
Qiao (2009)	96 (48/48)	54.0/54.0	A+M	M	600	21	C
Zhou (2009)	80 (40/40)	52.3/53.4	A+C	C	600	21	C

T, treatment group; C, control group; A, α-lipoic acid; M, methylcobalamin; P, prostaglandin E1; G, ginkgo biloba leaves injection; V, vitamin B1; L, ligustrazine; C, cilostazol.

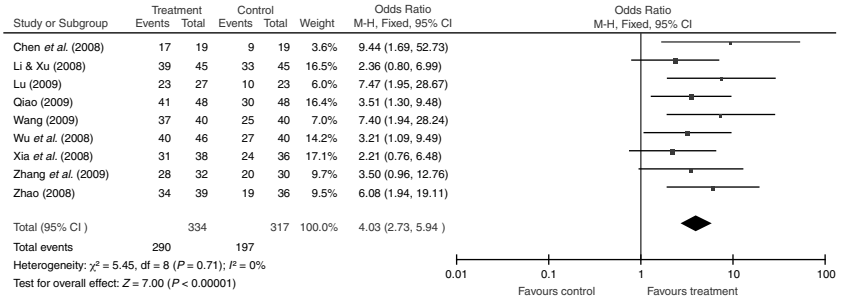

Figure 1 Comparison of efficacy of treatment group with control group for DPN.

Efficacy

Nine trials, with a total of 651 patients, investigated the efficacy of ALA (13, 16, 18, 19, 20, 23, 24, 25, 26). Figure 1 presents the result of the FE model for treatment group vs control group because heterogeneity between studies measured by the I^2 statistic or χ^2 test was insignificant ($P=0.71$, $I^2=0\%$). The treatment group was superior to the control group for efficacy improvement ($P<0.00001$, OR = 4.03, 95% CI (2.73, 5.94)).

Median MNCV

Ten trials investigated the median MNCV in a total of 756 patients (13, 14, 17, 18, 19, 20, 21, 22, 23, 27). Figure 2 presents the result of the RE analysis of treatment group vs control group because heterogeneity between studies was observed significantly ($P=0.0002$, $I^2=72\%$). Median MNCV increased significantly in the treatment group ($P<0.00001$, WMD = 4.63, 95% CI (3.58, 5.67)).

Median SNCV

Ten trials with a total of 754 patients investigated the median SNCV (13, 14, 17, 18, 19, 20, 21, 22, 23, 27). Figure 3 presents the result of the RE model for treatment group vs control group because heterogeneity between studies was significant ($P<0.00001$, $I^2=88\%$). A beneficial and statistically significant effect of ALA on median SNCV was observed ($P<0.0001$, WMD = 3.17, 95% CI (1.75, 4.59)).

Peroneal MNCV

Eight trials investigated the peroneal MNCV in a total of 613 patients (13, 16, 17, 18, 19, 20, 22, 27). Figure 4 presents the result of the RE analysis of treatment group vs control group because heterogeneity between studies was significant ($P<0.00001$, $I^2=86\%$). Compared with placebo, peroneal MNCV appeared to show a statistically significant improvement in the treatment group ($P<0.00001$, WMD = 4.25, 95% CI (2.78, 5.72)).

Peroneal SNCV

Six trials with a total of 462 patients investigated the peroneal SNCV (13, 17, 18, 20, 21, 27). Figure 5 presents the result of the RE model for treatment group vs control group because heterogeneity between studies was significant ($P<0.00001$, $I^2=89\%$). The treatment group was statistically superior to the control group for accelerating peroneal MNCV ($P=0.0009$, WMD = 3.65, 95% CI (1.50, 5.80)).

Adverse events

The most frequent side effects during the ALA treatment period were stomach upset (three cases) (27) and minor stretching (one case) (25). There was no withdrawal related to serious adverse events. We have not compared

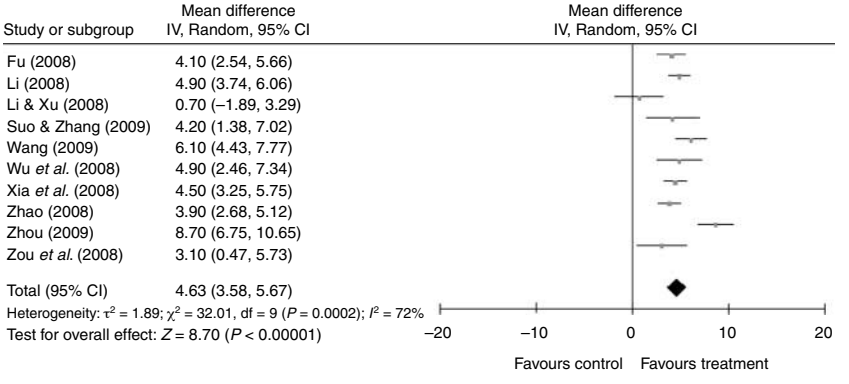

Figure 2 Comparison of median MNCV improvement of treatment group with control group for DPN.

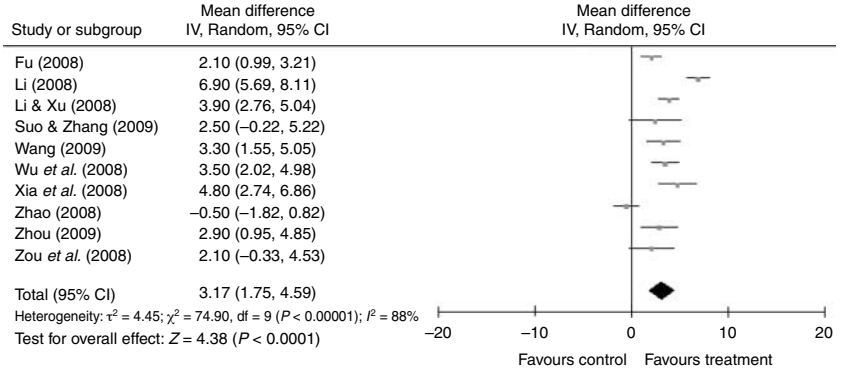

Figure 3 Comparison of median SNCV improvement of treatment group with control group for DPN.

the rate of adverse events because all studies did not report these events in detail.

Sensitivity analysis

As the FE and RE models produced similar estimates of treatment effect, the outcomes appear to be stable.

Publication bias

The 'funnel plot' showed that symmetry has indicated the least possible publication bias (Fig. 6).

Discussion

Diabetes mellitus is strongly associated with increased oxidative stress, which could be a consequence of either increased production of free radicals or reduced antioxidant defenses. The pathogenesis of DPN remains unclear. However, defects in metabolic and vascular pathways intersect with oxidative stress to produce the onset and progression of nerve injury in diabetic neuropathy. These pathways include: the production of advanced glycation end products; alterations in the sorbitol, hexosamine, and protein kinase C pathways; and activation of poly-ADP ribose polymerase. Multiple distinct metabolic pathways are impaired leading to a singular end result: enhanced cellular oxidative stress. Oxidative stress is particularly relevant to the risk of DPN, which appears to be mediated by reactive oxygen species. Additionally, oxidative stress leads to endothelial cell damage and vascular dysfunction. Furthermore, lipid peroxidation of nerve membrane has led to peripheral nerve ischemia and hypoxia. Overall, all the above changes result in faulty axon transport. The commonest abnormality in diabetes is the reduction of motor or sensory action potentials because of axonopathy. The nerve conduction velocity is gradually diminished in DPN, with estimates of a loss of 0.5 m/s per year (28). However, as an antioxidant, ALA directly terminates free radicals, inhibits peroxidation, increases endoneurial blood flow, and raises the reduced glutathione content of the peripheral nerve (3, 29, 30, 31). Thus, ALA exerts a beneficial effect on the vascular abnormalities of diabetes polyneuropathy and leads to an improvement in peripheral nerve function. ALA also increases insulin sensitivity (32). So ALA should be considered as a good choice among pathogenetically oriented treatments of diabetic neuropathy.

As ALA was first used therapeutically in Germany to treat diabetic neuropathy, there have been various controlled clinical trials assessing the efficacy of ALA in treating diabetic neuropathy (12, 33, 34, 35, 36, 37). The findings of ALADIN study substantiated that i.v. treatment with ALA using a dose of 600 mg/day over 3 weeks was superior to placebo in reducing symptoms of DPN (33). Following this short-term trial with ALA, a long-term response was investigated in the ALADIN II

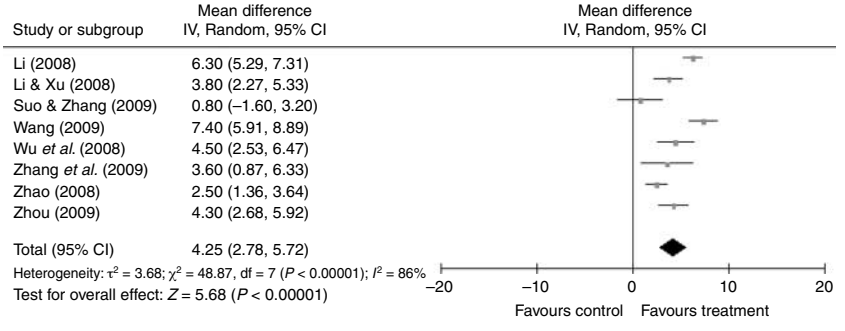

Figure 4 Comparison of peroneal MNCV improvement of treatment group with control group for DPN.

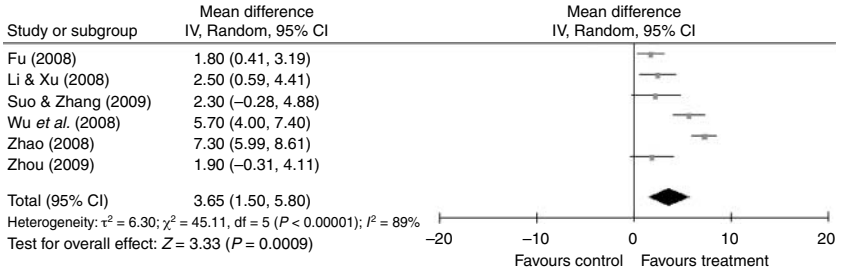

Figure 5 Comparison of peroneal SNCV improvement of treatment group with control group for DPN.

trial. Type 1 and 2 diabetic patients with symptomatic polyneuropathy were randomly assigned to three treatment regimens: i) 1200 mg ALA; ii) 600 mg ALA; and iii) placebo. ALA of 1200 or 600 mg or placebo was i.v. administered once daily for five consecutive days before enrolling the patients in the oral treatment phase of 2 years. In this trial, a beneficial and statistically significant effect of ALA on several attributes of nerve conduction was observed after 2 years of treatment (12). The ALADIN III study showed that a 3-week i.v. treatment with ALA followed by a 6-month oral treatment could not demonstrate a prior specified effect on neuropathic symptoms, but it indicated some clinically meaningful effects on neuropathic deficits in the treatment of ALA (34). However, the Oral Pilot (ORPIL) study, although with a smaller population, showed that oral treatment with 600 mg ALA t.i.d. for 3 weeks might improve symptoms and deficits resulting from polyneuropathy in type 2 diabetic patients (35). In the SYDNEY trial, diabetic patients were randomized to a parallel, double-blinded study of ALA (600 mg) or placebo and infused daily i.v. for 5 days per week for a total of 14 treatments. It appears to show an unequivocal and large beneficial effect of i.v. racemic ALA on the frequency and severity of the positive neuropathic sensory symptoms due to diabetic polyneuropathy (36). It was of particular interest that no significant adverse reactions in association with ALA were observed in the treatment of the above studies. However, the efficacy, safety, and dose response of treatment with ALA on DPN had not yet been established as SYDNEY α study was conducted. The SYDNEY α trial was a four-arm, parallel group, randomized, double-blind, placebo-controlled, multicenter trial using three oral doses of ALA (600, 1200, and 1800 mg q.d.) over 5 weeks after a 1-week placebo run-in period (37). The results of the SYDNEY II trial demonstrated that oral treatment with ALA over 5 weeks improved the positive sensory symptoms scored by the TSS in diabetic patients with distal symmetric polyneuropathy. It was notable that this overall effect was not dose dependent, as there were no differences in the changes in mean TSS among all active groups (37). The safety analysis revealed an overall favorable safety profile for the low dose. At higher oral doses, the rates of the gastrointestinal side effects were higher. The most frequent adverse event was a dose-dependent increase in the incidence of nausea. Whereas at ALA 600 mg q.d. this rate was slight (13%), it was markedly higher at 1200 and 1800 mg q.d., reaching 21 and 48% respectively (37). In summary, in the absence of a dose response and because the higher doses resulted in increased rates of gastrointestinal side effects, the results of SYDNEY α trial revealed that an oral dose of 600 mg once daily appeared to provide the optimum risk-to-benefit ratio (37).

The above trials reported clear subject improvement in symptom relief. But few of them showed objective improvement such as NCVs acceleration to assess the effects of ALA in treating DPN. Thus, our systematic review was performed on RCTs that used nerve conduction velocities as end points to assess effects in the treatment of DPN. This meta-analysis demonstrates that treatment with ALA given 300–600 mg i.v. per day for 2–4 weeks can significantly improve the conduction of median MNCV, median SNCV, peroneal MNCV, and peroneal SNCV for patients with DPN. Moreover, treatment with ALA does not give rise to severe adverse events.

However, there are some limitations to this meta-analysis. Most of the studies included in this review had poor methodological quality. These studies did not report the design, the randomization, and the concealment of randomization allocation. Most studies were of small sample size and did not describe withdrawals or dropouts. Even if the study referred to the withdrawal or

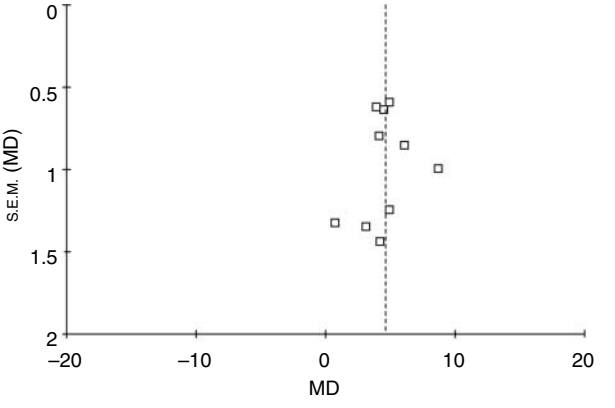

Figure 6 Funnel plot for treatment group vs control group. Dashed line indicates total summary odds. MD, mean difference.

dropout, it did not explain whether they performed the intention-to-treat analysis. Thus, the evidence of this meta-analysis may be not strong. In future, rigorously designed, randomized, double-blinded, placebo-controlled trials of ALA for DPN are needed to further assess the effect manifested as objective improvement in NCVs.

Based on the pooling of outcomes measured in randomized, controlled trials, we conclude that treatment with ALA (300–600 mg/day i.v. for 2–4 weeks) is safe and that the treatment can significantly improve both NCVs and positive neuropathic symptoms. However, the evidence may be not strong because most of the studies included in this meta-analysis have poor methodological quality.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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