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Alpha lipoic acid a boon for diabetic peripheral neuropathy: A systematic review and meta-analysis.

Pingali Usha Rani, Mekala Padmaja, Kammila Sireesha*, Penugonda Sravanasandhya

Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad, Telangana 500082, India

Abstract

Background: Diabetic Peripheral Neuropathy (DPN) is the most prevalent chronic microvascular complication in both type 1 and type 2 Diabetes Mellitus (DM) patients. In type 2 DM, insulin resistance affects vascular endothelium resulting in endothelial dysfunction, platelet hyperactivity and oxidative stress. Alpha Lipoic Acid (ALA) a potent antioxidant, targets oxidative stress in DPN which improves nerve blood flow, distal nerve conduction, and neuropathic symptoms. Herein, we planned to review the efficacy of ALA in improving symptoms of DPN without affecting glycaemic control.

Objective: To evaluate efficacy and safety of ALA on neuropathic symptoms in DPN.

Methods: A systemic search was conducted to collect and analyse all studies published from 1995 to 2020 that investigated effect of ALA on neuropathic symptoms in diabetic neuropathy patients using the phrase "Alpha lipoic acid and diabetic neuropathy". Studies were extracted from PubMed and CTRI. The Randomized Controlled Trials (RCT) which investigated effects of ALA in DPN patients were included whereas nonrandomized trials and clinical observations were excluded. The RevMan Manager 5.4 software was used for meta-analysis. The results were expressed as Weighted Mean Difference (WMD) with 95% confidence intervals (95% CIs) using a Fixed Effect (FE) or Randomized Effect (RE) model.

Results: Eight RCTs met inclusion criteria. Treatment group received ALA of 300-1800 mg per day and control group received a placebo. Compared with placebo, ALA showed significant improvement in symptoms of DPN. There were no serious adverse events during treatment period.

Conclusion: Our systemic review indicates a favourable effect of ALA on neuropathic symptoms in DPN patients.

Keywords: Alpha-lipoic acid, Diabetes mellitus, Diabetic peripheral neuropathy, Neuropathic symptoms, Platelet aggregation.

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Introduction

Diabetic neuropathy is the most prevalent chronic microvascular complication in both type 1 and type 2 Diabetes mellitus patients impacting their quality of life and causing considerable morbidity [1,2]. These patients have a sensory loss, motor deficits, and intractable neuropathic pain mostly affecting the feet. The common standard therapies available are tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, gabapentinoids and opioids. These drugs improve the neuropathic symptoms, but don't target pathogenetic mechanisms and are associated with several side effects [3]. Oxidative stress plays a pivotal role in the pathophysiology of diabetic neuropathy [4]. In Type 2 DM, insulin resistance affects vascular endothelium causing loss of sensitivity to Prostacyclin (PGI2) and Nitric Oxide (NO) resulting in endothelial dysfunction, platelet hyperactivity, oxidative stress and low-grade inflammation [5]. Platelet hyperactivity increases the risk of cardiovascular disease in T2DM.

Alpha lipoic acid is also known as thioctic acid, [6] a

very potent antioxidant. A recent literature survey reveals that treatment with α-lipoic acid not only improves nerve degeneration in diabetes but also is beneficial in other oxidative stress conditions like cataracts, radiation injury, and ischemia-reperfusion injury. It targets the oxidative stress in diabetic neuropathy which scavenges reactive oxygen species, reduces diabetic microvascular and macrovascular complications and improves nerve blood flow, distal nerve conduction as well as neuropathic symptoms [7].

Rationale

Alpha lipoic acid also inhibits platelet aggregation by different pathways of aggregation [7]. Adenosine Diphosphate (ADP) and Arachidonic Acid (AA) pathways are most sensitive to α-lipoic acid activity. The antiplatelet mechanism of action of ALA can be attributed to the formation of cAMP in platelets leading to inhibition of thromboxane A_2 (TXA_2), Calcium (Ca^{2+}) mobilization and protein kinase C alpha activation [6]. Despite its several benefits, safety and inexpensiveness, it is not widely used due to inadequate knowledge of its efficacy and safety. Recently several studies have been published that assessed the efficacy of ALA treatment in diabetic neuropathy by using various outcome parameters [6,8].

Considering the beneficial effect of ALA in the treatment of diabetic neuropathy, prompted us to perform a systematic review and meta-analysis of the effect of ALA in diabetic neuropathy. Herein, we delineate the review of efficacy of ALA in improving diabetic neuropathy symptoms like Total Symptom Score (TSS), Neuropathy Impairment Score (NIS), Neuropathy Disability Score (NDS) and Neurological Symptom Score (NSS).

Objective

To evaluate efficacy and safety of ALA on neuropathic symptoms in DPN.

Materials and Methods

Literature search strategy, and document retrieval

The Protocol is registered with Prospero (CRD42021284560). The study was reported as per Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA-2020) guidelines. A comprehensive and systematic search of the published literature for trials of ALA in the treatment of DPN was conducted from PubMed and Clinical Trials Registry-India (CTRI) databases from the year 1995 till 2020. A combination of Medical Subject Headings (MeSH) terms and free text was used, combined with Boolean logical operators to construct the search strategy. We did not use any restrictions in the electronic search for trials except for a language restriction (non-English languages were excluded). The reference list of each relevant publication was also examined to identify additional studies appropriate for inclusion in the meta-analysis. The 'keywords' used were 'alpha-lipoic acid', 'diabetic peripheral neuropathy, 'neuropathic symptoms', 'Total symptom score (TSS)', Neuropathy Impairment Score (NIS), Neuropathy Disability Score (NDS) and Neurological Symptom Score (NSS). The titles and abstracts were screened, and hand-searched for assessment of eligibility [9].

Eligibility criteria

Selection criteria were based on ALA dose, duration of therapy, control, and outcome criteria.

The RCTs evaluating the effect of ALA in DPN patients were included. The non-randomized trials, clinical observations, studies in a non-English language, and animal studies were not included.

Data extraction

Data were extracted based on patient baseline characteristics, study design, a daily dose of ALA and duration of treatment, control group and end points were abstracted. These data were independently extracted by two reviewers.

Quality assessment of individual studies

Version 2 of the Cochrane risk-of-bias tool for randomized trials was used to assess the risk of bias in randomized trials. RoB 2 was structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct, and reporting. Individual studies were evaluated based on the randomization process, deviation from the intended intervention, missing outcome data; measurement of the outcome and selection of the reported result. In each domain, the Risk of Bias (RoB) was classified into low, some concern or high for each RCT. The risk of bias assessments is tabulated in Table 1. Amongst the eight studies, seven studies by Ametov *et al.*, Ziegler *et al.*, Ziegler *et al.*, Ziegler *et al.*, Ruhnau *et al.*, Ziegler *et al.*, Reljanovic *et al.*, El-Nahas *et al.* [10-17] had a high risk of bias and only one study Ziegler *et al.* [12] had some concerns with biasness.

Outcome measures

The primary outcome measure considered for the review of ALA in DPN patients were improvement in the symptoms assessed by Total Symptom Score (TSS), Neuropathy Impairment Score (NIS), Neuropathy Disability Score (NDS) and Neurological Symptom Score (NSS) at the end of the therapy. Secondary outcomes were adverse events.

Statistical analysis

The RevMan Manager 5.4 software was used for the meta-analysis of pooled data. The Cochran's Q statistics, χ^2 and I^2 test were used to evaluate potential heterogeneity between studies (I^2>50% represents substantial heterogeneity). The Z test was used to estimate the statistical significance of pooled statistics.

Table 1. *Quality assessment of included studies (risk of bias).*

Outcomes	Study ID	D1	D2	D3	D4	D5	D6
TSS	Alexander S *et al.*, [10]	!	!	+	-	-	-
	D. Ziegler *et al.*, [11]	!	+	!	-	-	-
	Dan Z. *et al.*, [12]	+	+	+	+	!	!
	Dan Z. *et al.*, [13]	+	+	+	!	-	-
	K.J.Ruhnau *et al.*, [14]	+	+	+	+	-	-
NIS	Alexander S. *et al.*, [10]	!	!	+	-	-	-
	Dan Z. *et al.*, [12]	+	+	+	+	!	!
	Dan Z. *et al.*, [13]	+	+	+	!	-	-
	Dan Z. *et al.*, [15]	!	+	+	-	-	-
NDS	M. Reljanovic, *et al.*, [16]	+	+	-	+	+	-
	D. Ziegler *et al.*, [11]	!	+	!	-	-	-
	Mamdouh R. El-Nahas *et al.*, [17]	+	+	-	+	+	-
	K.J.Ruhnau *et al.*, [14]	+	+	+	+	-	-
NSS	D. Ziegler *et al.*, [11]	!	+	!	-	-	-
	Mamdouh R. El-Nahas *et al.*, [17]	+	+	-	+	+	-

+ Low Risk ! Some Concerns - High Risk

Summary of Findings

Outcomes	No. of patients		Effect (95% CI)	Certainty of the evidence (GRADE)
	ALA	PLACEBO		
Total Symptoms Score	345	346	**MD 1.73** (3.38 to 0.09)	⊕◯◯◯[a,b] VERY LOW
Neuropathy Impairment Score	485	475	**MD 0.41** (1.25 to 0.43)	⊕◯◯◯[b,c] VERY LOW
Neuropathy Disability Score	202	198	**MD 0.92** (2.43 to 0.59)	⊕◯◯◯ [a,b] VERY LOW
Neurological Symptom Score	163	166	**MD 1.21** (4.16 to 1.74)	⊕◯◯◯[b,d] VERY LOW

TSS: Total Symptoms Score; NIS: Neuropathy Impairment Score; NDS: Neuropathy Disability Score; NSS: Neurological Symptom Score; D1: Randomization process; D2: Deviations from intended interventions; D3: Missing outcome data; D4: Measurement of the outcome; D5: Selection of the reported result; D6: Overall Bias

Explanations

a: Heterogeneity between studies was significant 94%; **b:** Intervension duration vary among the studies

c: Heterogeneity between studies was significant 93%; **d:** Heterogeneity between studies was significant

The Inverse Variance (IV) method was used for the calculation of Mean Difference (MD) with 95% Confidence Intervals (CIs) for dichotomous variables using a Fixed Effect (FE) or Randomized Effect (RE) model where P<0.05 is considered as significant. A summary of the findings table was provided with key findings regarding the quality of evidence, the magnitude of effects of the interventions examined with the data on the outcomes by using the GRADE approach.

Results

Description of the studies

Searching PubMed and CTRI databases gave 284 results. Then, by manually reading the abstract, further screening was performed. 143 duplicates were subsequently removed. 133 results were excluded for being multiple interventions, animal studies, and different outcome measures. We finally selected 8 studies, and data were extracted from these 8 articles for this study (Figure 1). We screened 8 articles that met the inclusion criteria and have been selected for the meta-analysis which used TSS, NIS, NDS, and NSS to evaluate the effectiveness of ALA in the treatment of Diabetic Neuropathy compared to placebo.

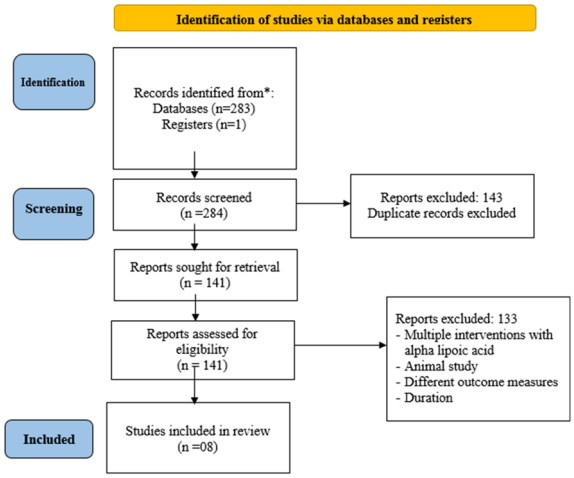

Figure 1. *Flow diagram showing preferred reporting items for systematic review and meta-analysis.*

Randomization process

Out of eight RCTs, five studies by Ziegler *et al.*, Ziegler *et al.*, Ruhnau *et al.*, Reljanovic *et al.*, Mamdouh *et al.*, [12-17] (62.5%) has well described the method for concealment of allocation and were having a 'low risk of bias' in this domain. The remaining 3/8 (37.5%) RCT had 'some concerns in RoB' as they haven't described properly about the allocation concealment method Alexander *et al.* [10], Ziegler *et al.* [11] and Ziegler *et al.* [15].

Deviations from intended interventions

Only 1/8 of (12.5%) studies Alexander *et al.* [10] had 'some concerns in RoB' with regards to deviations from intended interventions as there were some deviations from intervention used in the study. In the remaining seven (87.5%) studies, the deviations were minimum and refereed as 'high RoB'.

Missing outcome data

A total of 5/8 studies (62.5%) studies Ametov *et al.*, [10] Ziegler *et al.*, [12], Ziegler *et al.*, [13], Ruhnau *et al.*, [14], Ziegler *et al.*, [15] had 'low RoB' with regards to missing outcome data. One study Ziegler *et al.*, [11] (12.5%) had 'some concerns in RoB' and the remaining two studies Reljanovic *et al.*, [16], Mamdouh *et al.*, [17] (25%) did have a high attrition rate and did not mention the handling of missing data and were judged as 'high RoB'.

Measurement of the outcome

A total of 4/8 (50%) studies Ziegler *et al.*, [12], Ruhnau *et al.*, [14], Reljanovic *et al.*, [16], Mamdouh *et al.*, [17] had 'low RoB' in this domain. One study Ziegler *et al.*, [13] (12.5%) had 'some concerns in RoB' and the remaining three studies Alexander *et al.*, [10], Ziegler *et al.*, [11], Ziegler *et al.*, [13] (37.5%) had 'high RoB'.

Selection of the reported result

A total of 5/8 (62.5%) studies Ametov *et al.*, [10], Ziegler *et al.*, [11], Ziegler *et al.*, [13], Ruhnau *et al.*, [14], D Ziegler *et al.*, [15] had 'high RoB' with regards to 'Selection of the reported results' since all the outcome measures were not reported. In one study Ziegler *et al.*, [12] (12.5%) had 'some concerns in RoB'. The remaining two studies Reljanovic *et al.*, [16], Mamdouh *et al.*, [17] (25%) had 'low RoB'.

Grading of quality of evidence

The quality of evidence in efficacy outcome was measured as very low due to varied distinctions and inconsistencies in point estimates with high heterogeneity as well as the use of the different duration of alpha lipoic acid among the studies. The overall result (95% CI) fails to exclude the important benefit. Table 2 reviews the summary of the findings (GRADE pro).

Effects of interventions

Efficacy assessment: To determine the efficacy of ALA in DPN patients, eight randomized double-blind placebo-controlled trials, the SYDNEY, ALADIN, ALADIN III, SYDEY 2, ORPIL, NATHAN 1, ALADIN II and ALA 2020 studies, [10-17] comprising a total of 1360 people were investigated based on the outcomes like TSS, NIS, NDS, and NSS (see Table 2, for summaries of the studies). The study populations included individuals ranging in age from 18 to 74 years with type 1 and 2 Diabetes Mellitus. The studies took place in inpatient and outpatient treatment centres at Germany, Russia, Croatia and Egypt. Amongst these 08 articles, some analysed the efficacy based on different endpoint outcomes.

Total Symptoms Score (TSS)

Five trials including 345 patients in the ALA treatment group and 346 in the placebo control group investigated the Total Symptoms Score (TSS) [10-14]. Table 2 shows

the characteristics of the studies on ALA treatment compared to placebo, the outcome parameter was the Total Symptoms Score (TSS). Figure 2 The Forest plot obtained as a result of the RE analysis of the ALA treatment group *vs.* the placebo group. Heterogeneity between studies was significant (χ^2=65.27, P<0.00001, I^2=94%). Compared with placebo, Total Symptoms Score (TSS) appeared to show a statistically significant improvement in the ALA treatment group (Z=2.07, P=0.04, WMD=1.73, 95% CI (-3.38, -0.09)).

Neuropathy Impairment Score (NIS)

Four trials including 485 patients in the ALA treatment group and 475 in the placebo control group investigated the Neuropathy Impairment Score (NIS) [10,12,13,15]. Table 2 shows the characteristics of studies on ALA treatment compared with placebo, using Neuropathy Impairment Score (NIS) as an outcome measure. Figure 3 is the Forest plot obtained as a result of the FE analysis of the ALA treatment group *vs.* placebo control group. Heterogeneity between studies was significant (χ^2 =45.08, P<0.00001, I^2=93%). Compared with the placebo, the Total Symptoms Score (TSS) was improved in the ALA group. (Z=0.96, WMD=-0.41, 95% CI (-1.25, 0.43)). However, the result was not statistically significant (P=0.34).

Neuropathy Disability Score (NDS)

Four trials including 202 patients in the ALA treatment group and 198 patients in the placebo control group evaluated the efficacy using the Neuropathy Disability Score (NDS) [15,10,16,13]. Table 2 shows the characteristics of studies on ALA treatment compared to placebo; the outcome measure was Neuropathy Disability Score (NDS). Figure 4 is the forest plot obtained as a result of the RE analysis of the ALA treatment group vs placebo control group. Heterogeneity between studies was significant (χ^2=51.42, P<0.00001, I^2=94%). Compared with the placebo, Neuropathy Disability Score (NDS) was improved in the ALA treatment group. (Z=1.19, WMD=-0.92, 95% CI (-2.43, 0.59)). However, the result was not statistically significant (P=0.23).

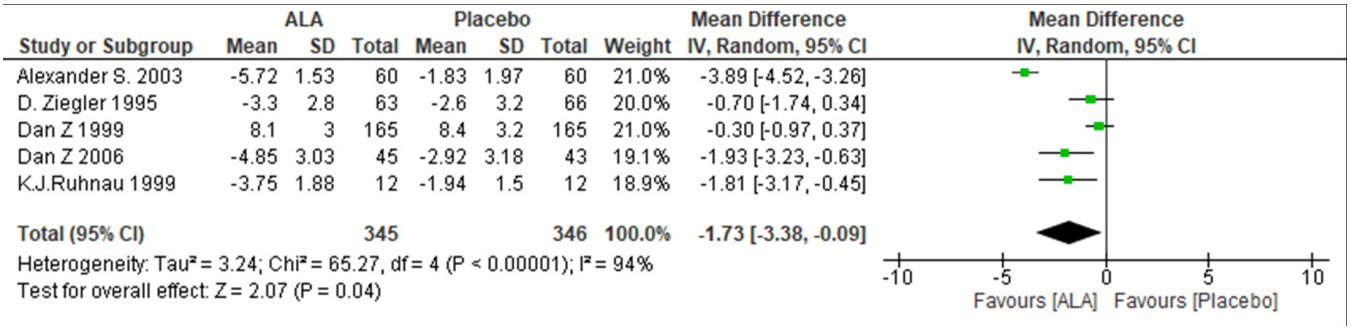

Figure 2. *Forest plot of comparison of Total Symptoms Score (TSS) in ALA group with placebo group.*

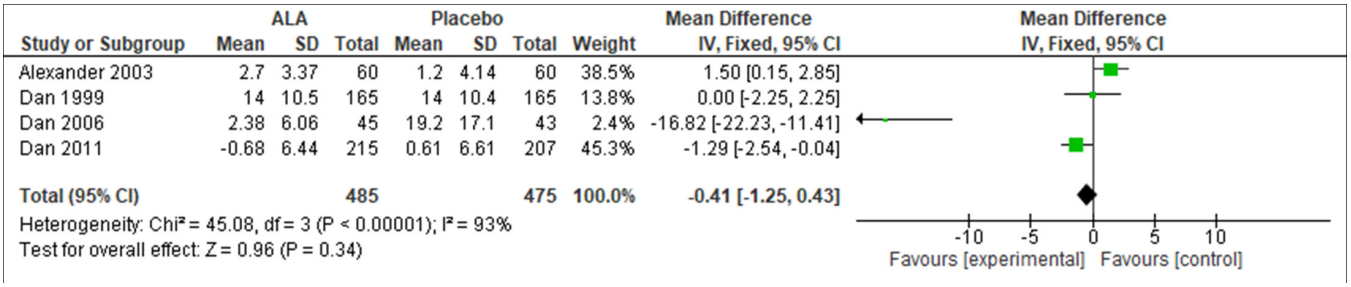

Figure 3. *Forest plot of comparison of Neuropathy Impairment Score (NIS) in ALA group with placebo group.*

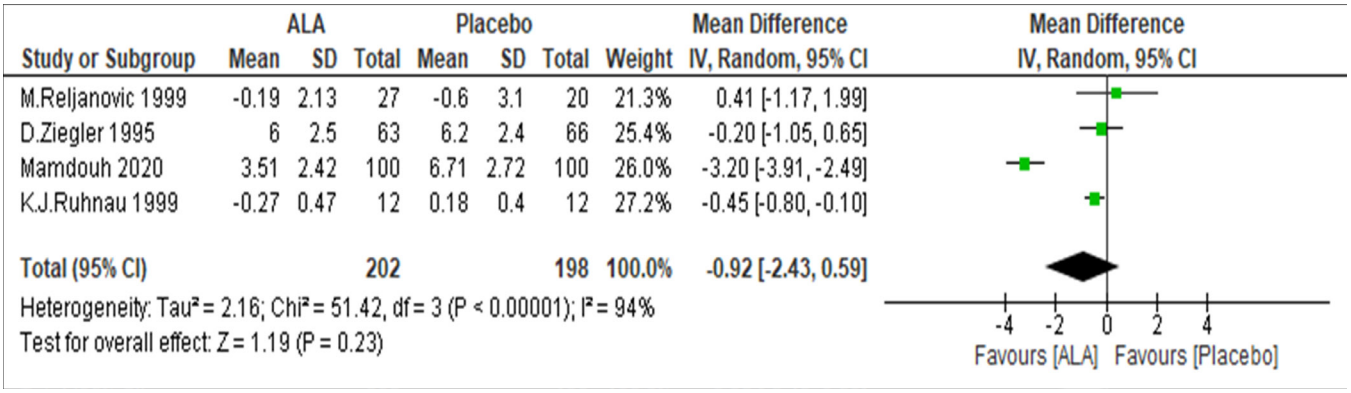

Figure 4. *Forest plot of comparison of Neuropathy Disability Score (NDS) in ALA group with a placebo group.*

Table 2. *Characteristics of included studies.*

Study Duration	Sample Size (n)		Age (Yrs) Mean ± SD		Gender (M/F)		BMI (Kg/m²) Mean ± SD		Total Symptom Score (TSS) Mean ± SD		Neuropathy Impairment Score (NIS) Mean ± SD		Neuropathy Disability Score (NDS) Mean ± SD		Neurological Symptom Score (NSS) Mean ± SD	
	ALA 600 mg	Placebo	ALA 600 mg	Placebo	ALA 600 mg	Placebo	ALA 600 mg	Placebo	ALA 600 mg	Placebo	ALA 600 mg	Placebo	ALA 600 mg	Placebo	ALA 600 mg	Placebo
3 Weeks	60	60	56.8 ± 9.65	55.4 ± 8.66	M:23.3% F:76.6%	M:40% F:60%	29.4 ± 4.93	29.3 ± 5.23	-5.72 ± 1.53	-1.83 ± 1.97	2.7 ± 3.37	1.2 ± 4.14				
3 Weeks	63	66	57.5 ± 8.7	60.2 ± 7.7	M:37% F:63%	M:35% F:65%	27.7 ± 4.9	29.7 ± 4.9	-3.3 ± 2.8	-2.6 ± 3.2			6.0 ± 2.5	6.2 ± 2.4	5.6 ± 2.02	5.3 ± 1.7
7 Months	165	165	56.5 ± 7.1	57.3 ± 5.5	M: 45.5% F: 54.4%	M: 50.3% F: 49.7%	29.0 ± 4.8	29.5 ± 4.8	8.1 ± 3.0	8.4 ± 3.2	14.0 ± 10.5	14.0 ± 10.4				
6 weeks	45	43	56 ± 12	57 ± 11	M: 44% F: 56%	M: 35% F: 65%	28.7 ± 3.9	29.1 ± 4.4	-4.8 ± 3.03	-2.92 ± 3.18	2.38 ± 6.06	19.2 ± 17.1				
3 Weeks	12	12	60.5 ± 6.9	62.1 ± 4.5	M:50% F:50%	M:50% F:50%	29.6 ± 4.0	28.5 ± 3.9	-3.75 ± 1.88	-1.94 ± 1.50			-0.27 ± 0.47	0.18 ± 0.4		
4 Years	215	207	53.3 ± 8.3	53.9 ± 7.6	M: 66.1% F: 33.9%	M: 67.0% F: 33.0%	29.7 ± 6.1	29.8 ± 6.1			-0.68 ± 6.44	0.61 ± 6.61				
24 Months	27	20	58.1 ± 17.3	57.3 ± 6.4	M:40.75% F:59.25%	M:50% F:50%	29.7 ± 3.5	28.3 ± 3.4					-0.19 ± 2.13	-0.6 ± 3.1		
6 Months	100	100	54.1 ± 8.2	52.7 ± 7.1	M:38% F:62%	M:40% F:60%	33.7 ± 4.7	32.2 ± 5.7					3.51 ± 2.42	6.71 ± 2.72	2.95 ± 2.50	5.66 ± 0.92

Neurological Symptom Score (NSS)

Two trials including 163 patients in the ALA treatment group and 166 in the placebo control group investigated the Neurological Symptom Score (NSS) [11,17]. Table 2 shows the characteristics of studies on ALA treatment compared to placebo, the outcome measure was Neurological Symptom Score (NSS).

Discussion

Diabetic Peripheral Neuropathy (DPN) is the most prevalent chronic complication of both type 1 and type 2 diabetes mellitus [18]. Chronic hyperglycaemia results in insulin resistance, increased oxidative stress, and platelet dysfunction and plays a key role in the pathogenesis of DPN [19]. Enhanced flux through the polyol pathway, glucose auto-oxidation, and accumulation of advanced glycation end-products are thought to cause oxidative stress, which downregulates Na-K-ATPase activity. This results in nerve ischemia causing motor and sensory nerve fibres injury. Hyperglycaemia also damages the myelin membrane structure and neurosecretory system. Typical symptoms of DPN are symmetric numbness, paraesthesia, or pain in the distal lower limbs. Patients with uncontrolled blood sugar levels for long periods result in foot ulceration and Charcot neuroarthropathy [20]. It has also been linked that increased free-radical production along with defective antioxidant mechanisms can generate DPN.

Our systemic review was performed on 8 RCTs with oral/ intravenous ALA 300-1800 mg/per day and placebo control, using different neuropathy symptom scores like TSS, NIS, NDS, and NSS as efficacy outcome measures, to assess the efficacy of Alpha Lipoic Acid in diabetic neuropathy. In this meta-analysis, we found that there was a statistically significant improvement in the Total Symptoms Score (TSS) in the ALA treatment group (P=0.04) whereas no statistically significant difference was found in Neuropathy Impairment Score (P=0.34), Neuropathy Disability Score (P=0.23) and Neurological Symptom Score (P=0.44). Overall, this meta-analysis concluded that the treatment with ALA 600 mg/day can significantly improve the neuropathic symptoms in DPN patients.

In ALADIN Study [11] ALA was given intravenously 100 mg, 600 mg and 1200 mg for 3 weeks in DPN patients. There was a significant difference in TSS from baseline to 3 weeks in ALA 600 mg group and 1200 mg group. The incidence of adverse events was more in ALA 1200 mg group compared to ALA 600 m and ALA 100 mg. In ALADIN III Study [12] ALA was administered intravenously 600 mg for 3 weeks followed by 600 mg orally t.i.d for 6 months and they found a reduction in the TSS compared to placebo from baseline to 6 months. The Oral Pilot (ORPIL) study showed improvement in the neuropathic symptoms with ALA 600 mg given orally for 3 weeks compared to placebo. In SYDNEY Trial [10] the patients were randomized to ALA 600 mg and placebo were given intravenously five times a week for 14 treatments. There was a significant decrease in TSS from baseline. Ziegler *et al.*, [13] conducted a study in DPN patients with ALA 600 mg, 1200 mg and 1800 mg once daily for 5 weeks, after a run-in period of 1 week. They found that there was a reduction in TSS from baseline in all the groups, but no difference was found between the groups. The incidence of adverse events was dose-dependent with the highest adverse events reported in the 1800 mg group. The NATHAN 1 trial [15] showed clinically meaningful improvement in NIS with ALA 600 mg orally once daily compared to placebo. El-Nahas *et al.*, [17] found significant results in outcome parameters (NSS and NDS) with ALA 600 mg twice daily compared to placebo.

However, the evidence may be not strong as there are some limitations to be considered in this meta-analysis. Some of the studies included in the meta-analysis are of poor methodological quality, lack randomization allocation details, have small sample size, no description of withdrawals or dropouts. In future, rigorously designed, randomized, double-blinded, placebo-controlled trials of ALA are needed to further evaluate the efficacy in reducing diabetic neuropathy symptoms.

Conclusion

Based on our systemic review and meta-analysis, we found that ALA has improved DPN clinical symptoms compared to placebo. The ALA treatment groups showed a significant decrease in the TSS, NIS, NDS, and NSS scores. Hence, from these results, it is evident that ALA may be used as an effective, and safe therapy for patients with DPN.

Conflict of Interest

The authors declare no conflicts of interest.

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***Correspondence to:**

Kammila Sireesha

Department of Clinical Pharmacology and Therapeutics

Nizam's Institute of Medical Sciences

Hyderabad

Telangana 500082

India