Efficacy of Using Alpha-Lipoic Acid Supplement in Patients with Diabetic Neuropathy: A Meta-Analysis and Systematic Review

Dr. Kholoud Eid Albeladi
Family Medicine Resident, Prince Sultan Military Medical City in Riyadh, Saudi Arabia

Dr. Shorug Khalid Abdulaziz Alwayili
Family Medicine Resident, Prince Sultan Military Medical City in Riyadh, Saudi Arabia

Prof. Mostafa Kofi
Consultant, FCM Dept, PSMMC, Prince Sultan Medical Military City in Riyadh, Saudi Arabia

Abstract

Background: In the 21st century, diabetes mellitus and its complications have become the most common health-care problem. The most common complication is diabetic neuropathy. Many drugs were tried to alleviate the neurological symptoms, whereas Alpha-lipoic acid has proven its effectiveness.

Aim: We aim in our study to assess the efficacy of Alpha-lipoic acid versus other lines in diabetic patients complicated with neuropathy.

Methods: We searched online databases such as (PubMed, Scopus, WOS, and Cochrane Library) for related randomized clinical trials (RCTs). Retrieved articles were screened, and relevant studies were included in a meta-analysis. Continuous data were pooled as mean difference (MD) with 95% confidence interval (CI), and dichotomous data were pooled as relative risk (RR) and 95% CI. Analysis was conducted using RevMan software (Version 5.4). Our primary outcome was the alleviation of neurological symptoms, while the 2nd outcome was the occurrence of adverse events.

Results: Four RCTs (358 cases) were included. ALA treatment produced favorable results for TSS (a dose-related trend was observed), NDS. ALA treatment resulted in a dose-dependent response relative to the placebo for TSS and the global satisfaction score. The use of ALA to prevent neurological symptoms should be further researched.

Conclusion: Alpha-lipoic acid has a satisfactory effect on neurological symptoms, there was a marked decrease in sensory symptoms.

Introduction

It is thought that the total number of diabetic patients will be doubled by 2030, reaching a pandemic level of 366 million people [1]. The 21st century has witnessed many health-care problems including diabetic polyneuropathy which is a condition that incorporates a wide variety of clinical pathologies curtailed from peripheral nervous system dysfunction. The prevalence of diabetic polyneuropathy is approximately 50% of the total diabetes complications and the symptoms include various presentations like symmetrical sensory-motor neuropathy, polyradiculopathy, and plexopathy [2]. Several risk factors influence the progression of diabetic neuropathy, including the duration of diabetes, poor glycemic control, and obesity. The mechanism of diabetic neuropathy is not fully understood despite the research on this topic, and a disease-modifying treatment for this condition is yet to be developed [3].

Alpha-lipoic acid (ALA) is a caprylic acid-derived antioxidant that is synthesized in the mitochondria. Studies reported that ALA improved nitric-oxide-mediated endothelium-dependent vasodilation in patients with diabetes and improved microcirculation.
in patients with diabetic polyneuropathy [4]. Researchers have extensively studied the neuroprotective effects of ALA, which are achieved through reducing oxidative stress and increasing microcirculation [4]. However, the results pertaining to the optimal administration method and dosage have been inconclusive.

Given the growing body of evidence concerning the role of α-lipoic acid in the treatment of diabetic neuropathy, this systematic review aims to evaluate the current literature and make recommendations for further research. The focus is on symptom reduction and the incidence of adverse events following administration of α-lipoic acid in this population.

**Methods**

This systematic review and meta-analysis followed the steps described in the "Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)" and in the "Cochrane handbook for systematic reviews of interventions" [5].

**Data collection and Search Strategy**

We searched PubMed, Scopus, Web of Science, and Cochrane library databases for published RCTs from January 2019 till December 2023. We used the following keywords: diabetes, alpha-lipoic acid; diabetic polyneuropathy, polyneuropathy.

**Inclusion and Exclusion Criteria**

For study selection, the following inclusion criteria set the parameters for eligibility: (1) diabetic patients with neuropathy, (2) trials studying effect of α-lipoic acid, (3) and proper contrast was done in the study. Studies were excluded if they were published in a language other than English, incomplete, and animal studies. Title, abstract, and full text screening was done for final decision to be included. Also, unpublished studies, literature, and conference studies were excluded.

**Screening and Study Selection**

Retrieved records were imported to Endnote software, and duplicates were removed. The remaining records underwent title and abstract screening then full-text screening according to our eligibility criteria. Two reviewers performed the screening process independently, and any disagreement was solved by discussion. Eligible articles were included in the meta-analysis.

**Data Extraction**

All study authors shared in the data extraction. The extraction included author(s), year of publication, patient population, intervention, comparison, study period, outcome measures, results, and any conclusions deduced based on the evidence provided regarding the administration of α-lipoic acid among diabetic patients with symptoms of peripheral neuropathy.

**Quality Assessment**

According to the Cochrane Collaboration tool for risk of bias assessment in randomized studies, we evaluated the quality of the included studies (6). The tool included the judgment of the selection, performance, detection, attrition, reporting, and other bias domains. Each domain was judged as low, high, or unclear risk of bias. At least two independent reviewers judged each domain and conflicts were solved by discussion.

**Statistical Analysis**

Data analysis was conducted using RevMan software version 5.4. Data of continuous outcomes were reported as mean difference (MD) and 95% confidence interval (CI) using the Inverse-Variance method, and dichotomous data were reported as relative risk (RR) and 95% CI using the Mantel-Haenszel method. We assessed heterogeneity using chi-square and I-square tests, and heterogeneity was considered significant at chi-square P-value < 0.1 and I² > 50%. We used the random-effects model for analysis. Whenever pooled data are heterogeneous, we tried to solve the heterogeneity by sensitivity analysis using the leave-one-out test and subgroup analysis.

**Results**

**Literature Search and Study Selection**

Searching electronic databases yielded a total of 119 articles. After removing duplicates, we had 58 unique articles that underwent title and abstract screening. Of these articles, 37 were excluded, and 21 full texts were retrieved and screened according to our eligibility criteria. Finally, 4 studies were considered eligible for inclusion in the meta-analysis. Figure 1 summarizes the flow of the study selection process and data collection.

**Characteristics of the included studies**

Included studies were performed in various countries. The sample size varied considerably across studies, ranging from 24 to 200. The follow-up period varied from five weeks in some studies to six months in other studies. The mean age of included patient groups ranged from 24 to 57 years. Tables 1 show the summary of included studies and the baseline characters of included patients.
Records identified through database searching (n = 119)→ Duplicates removed. (n = 61)

Records after duplicates removed (n = 58)→ Records screened (n = 58)→ Records excluded (n = 37)

Full-text articles assessed for eligibility (n = 21)→ Full-text articles excluded (n = 17)

Studies included in qualitative synthesis (n = 4)

Tables 1: Summary of Included Studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Author (year)</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Study period</th>
<th>Outcome measures</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>[7]</td>
<td>Won 2020</td>
<td>24 cases</td>
<td>ALA caps with a dose (1,663 mg/day)</td>
<td>placebo</td>
<td>five weeks on two periods</td>
<td>Treatment-adverse events, pain severity</td>
<td>No significant differences (p = 0.7) in pain intensity or noted side effects</td>
<td>No beneficial effect of ALA in treatment of diabetic neuropathy</td>
</tr>
<tr>
<td>[8]</td>
<td>Nahas 2020</td>
<td>200 cases</td>
<td>ALA caps with a dose (600-mg)</td>
<td>placebo</td>
<td>Six months, measurement assessed at months 1, 3, and 6</td>
<td>neurological symptoms, pain severity</td>
<td>ALA-treated patients had significantly improved outcome</td>
<td>Oral ALA two times/day over 6-months was effective, safe, and tolerable in the treatment of diabetic neuropathy</td>
</tr>
<tr>
<td>[9]</td>
<td>Siddiqui 2021</td>
<td>110 cases</td>
<td>ALA caps with a dose (600-mg)</td>
<td>placebo</td>
<td>24 weeks</td>
<td>neurological symptoms, pain severity</td>
<td>There is significant improvement</td>
<td>ALA has favorable effect on</td>
</tr>
</tbody>
</table>
Quality assessment
Most included studies had a low risk of selection bias regarding both selection bias domains: random sequence generation and allocation concealment. However, the remaining studies were of unclear risk of selection bias because the reported data are insufficient to judge. Detection bias was at low risk in most studies due to proper blinding of the outcome assessor. Attrition bias was at low risk in most studies because the lost data are insufficient to produce bias results. Reporting bias was judged low risk in most studies because the outcomes of interest were reported as expected. The “other bias” domain was judged low risk in most studies and unclear in some studies. The risk of bias graph shows the overall judgment of each risk of bias domain figure 2.

Outcomes
Total symptoms improvement
All the included RCTs studied TSS outcomes (5, 8–10). The pooled estimated effect, which was determined using a fixed-effect model, revealed that ALA administration led to significantly more favorable TSS outcomes relative to the control (MD, -6.63; 95% CI [-9.78, -3.48]). The shortest administered duration of the studies is 5 weeks and the longest is for 24 weeks. In this outcome, there are two studies that administered ALA at 600 mg/day, and two study administered 1,663 mg/day. The heterogeneity of the studies was significant (p < 0.01). Furthermore, ALA administration produced favorable effects that exhibited dose-related trends (figure 3).
Improvement of neurological symptoms

Three of the included RCTs reported NDS outcomes (8-10). The estimated effect, which was determined using a fixed-effect model, revealed that ALA administration produced significantly more favorable NDS outcomes relative to the control (MD, −5.32; 95% CI [-9.78, -3.48] Figure 4). The administered durations are 5 weeks and 24 weeks. In this outcome, there is one study that administered ALA at 1,663 mg/day, and two study administered 600 mg/day.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>ALA</th>
<th>placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
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</thead>
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<tr>
<td>Nimesh 2020</td>
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<td>200</td>
<td>18</td>
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<tr>
<td>Oliner 2021</td>
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<td>117</td>
<td>24</td>
<td>25</td>
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<tr>
<td>Bedregal 2021</td>
<td>5</td>
<td>106</td>
<td>110</td>
<td>9</td>
</tr>
</tbody>
</table>

Total (95% CI)

Heterogeneity: Chi² = 2.57, df = 2 (P = 0.28); I² = 22%
Test for overall effect: Z = 2.67 (P = 0.003)

Figure 4: Weighted Mean Difference in Role of Alpha-Lipoic Acid Versus Other Lines in Improvement of Neurological Symptoms. Abbreviations: CI, confidence interval; IV, inverse variance; SD, standard deviation

Discussion

Diabetes-related neuropathy cannot currently be cured; instead, it can only be controlled by reducing the condition’s rate of development, easing its associated discomfort, and treating any consequences. It is advised to improve glycemic management and make lifestyle changes in order to slow the growth of diabetic neuropathy (11). Several pharmacological treatments (gabapentin, pregabalin, and mirogabalin) are advised in the Oral and Topical Management of Severe Diabetic Polyneuropathy in order to alleviate the pain caused by this condition (12).

The ultimate benchmark for impartially evaluating diabetic neuropathy has not yet been created due to the disorder’s heterogeneous character. Current testing methods, including monofilament and sensory testing (pinprick, vibration, and temperature), rely on the operator’s performance, and there is currently no established protocol for documenting the findings in follow-up testing (13).

In order to compare the effectiveness of MC (500–1000 mg, intravenous or intramuscular administration) and lipoic acid (300–600 mg), administered intravenously or intramuscularly, against MC alone, a study was carried out in 2013 with 1106 patients. The study’s findings suggested that giving ALA for two to four weeks was linked to better outcomes for neuropathic pain and NCS. The results of ALA-alone therapy taken orally, however, are still unknown (14).

A meta-analysis on four studies by Mijnhout found that intravenous (IV) ALA treatment at a dose of 600 mg/day for a three week period significantly lowered the total symptoms score; however, the meta-analysis did not examine the effects of ALA delivered orally (4).

Strengths and Limitations

In this systematic review and meta-analysis, we included RCTs only to provide high-quality evidence and followed the widely accepted PRISMA guidelines during the conduction of this study. We included all published RCTs related to our topic. Limitations in this study include the heterogeneity detected in many outcomes and could not be solved in some cases. In addition, some long-term outcomes were reported by a small number of studies, which limits the generalizability of the results.

Conclusion

Alpha-lipoic acid has a satisfactory effect on neurological and other diabetic symptoms.

Declarations of Interest

None

Source of Funding

None

Acknowledgment

None

References

reporting systematic reviews. BMJ. 2021 Mar 29;372:n71. doi: 10.1136/bmj.n71


