Original Research Article

# Add-on Vitamin E in Improving Treatment Outcomes in Diabetic Peripheral Neuropathy: A Prospective Interventional Study

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**Abstract**

**Background:** Neuropathy is one of the most common long-standing complications of diabetes, affecting over 50% of the diabetic individuals. Managing DPN and its complications involves comprehensive care and a multidisciplinary approach. Besides pharmacological treatments, botanicals and dietary supplements that have also been found to improve symptoms of DPN without affecting glucose control. The possible role of vitamin E in the management of DPN have been postulated in various studies. The present study thus aimed to prospectively assess whether add-on treatment with vitamin E can improve treatment outcomes in diabetic peripheral neuropathy.

**Methods:** The study included newly diagnosed patients with diabetic peripheral neuropathy for a period of initial two months. Patients were randomly allocated to either standard treatment Group (Group A) or the intervention Group (Group B). As a part of intervention, patients received vitamin E 400mg once daily in addition to the standard of care. Efficacy Parameters measured at baseline, 6 months and 12 months included changes in visual analog scoring, mean pain score, brief pain inventory and patient's global impression of change. Treatment safety, quality of life and treatment adherence was assessed. Data was statistically analysed.

**Result:** The study included a total of 100 patients, 50 patients in each Group. Significantly higher decrease of glycaemic measures was noted for Group B compared to Group A in terms of PPPG and serum creatinine, however, there was comparable change in HbA1c and FPG for both Groups. There was comparable significant reduction in mean VAS scoring at 6 and 12 months for Group B. Considering all the efficacy measures, there was highest reduction for the pain interference in the intervention arm (Group B), in comparison to Group A. ($p<0.001$). Quality of life measures and mean adherence scoring significantly increased for treatment group B as compared to A at both 6 months and 12 months of study assessments. No major safety concerns were reported during the study period.

**Conclusion:** Our study noted that addition of vitamin E as an added supplementation to the standard of care showed benefits in terms of patient reported reduced pain interference and pain perception, which also significantly improved overall quality of life in these patients.

**Key Words:** Vitamin E, Diabetic Peripheral Neuropathy, Add-on Treatment

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## Introduction

Neuropathy is one of the most common long-standing complications of diabetes, affecting over 50% of the diabetic individuals. [1] Diabetic peripheral neuropathy (DPN) refers to nerve damage that occurs specifically in the peripheral nerves of individuals with diabetes. It is a common complication of diabetes, especially in those with poorly controlled blood sugar levels over an extended period. DPN can lead to various complications. Nerve damage can cause loss of sensation in the feet, making it difficult to detect injuries, cuts, or ulcers. Without proper sensation, minor wounds can go unnoticed and develop into serious infections or ulcers. Poor blood circulation due to diabetes can further hinder the healing process, potentially leading to foot ulcers, gangrene, and, in severe cases, amputation. Peripheral neuropathy can also affect balance and coordination, increasing the risk of falls and related injuries. Charcot joint, also known as neuropathic arthropathy, is a condition where the joints, typically in the feet, deteriorate due to nerve damage, which can further result in joint deformities, instability, and chronic pain. DPN can also affect the autonomic nervous system, which controls involuntary bodily functions. This can lead to complications such as gastrointestinal problems (e.g., gastroparesis, constipation, diarrhoea), bladder dysfunction, sexual dysfunction, abnormal heart rate, and changes in blood pressure. DPN can lead to increased susceptibility to infections. Nerve damage can impair the normal function of sweat glands, leading to dry skin that is prone to cracking and infections. In addition, the weakened immune response associated with diabetes can further increase the risk of infections. DPN often presents with symptoms such as tingling, numbness, burning sensations, or sharp pain in the affected areas. This chronic pain can significantly impact a person's quality of life and daily activities. [2-8]

Managing DPN and its complications involves comprehensive care and a multidisciplinary approach. Treatment strategies may include maintaining optimal blood sugar control, pain management, regular foot care, physical therapy, exercises, treating underlying conditions contributing to neuropathy, such as hypertension or high cholesterol and managing autonomic symptoms through medications, dietary changes, and lifestyle modifications. Numerous pharmacological treatments including antidepressant, anticonvulsant, analgesic, and topical medications - have been used to reduce the pain associated with DPN and to improve patients' quality of life. [9] It is important for individuals with diabetic peripheral neuropathy to work closely with their healthcare professionals to develop a personalized treatment plan and to address any complications promptly to minimize their impact on daily life and long-term health.

Alternatively, botanicals and dietary supplements that have also been found to improve symptoms of DPN without affecting glucose control include Evening Primrose oil, alpha-lipoic acid, capsaicin, and vitamin E. The possible role of vitamin E in the management of DPN may be attributed to the concept of oxidative stress and antioxidant treatment. [10] Some researchers have shown that defective nerve conduction in diabetic subjects with mild-moderate peripheral neuropathy may be improved by pharmacological doses of vitamin E supplementation. [11] In a randomized, double-blind, placebo-controlled trial, evaluating the effect of vitamin E on nerve function in type 2 diabetic subjects with mild-to-moderate neuropathy, significant symptom reduction was noted. [12] The present study thus aimed to prospectively assess whether add-on treatment with vitamin E can improve treatment outcomes in diabetic peripheral neuropathy.

## Methodology

A prospective interventional study was conducted in eastern India for a period of one year. Permission for the conduct of the study was obtained from the institutional ethics committee and written informed consent was obtained from each participating subject in the study. Patients were randomly allocated to either standard treatment Group (Group A) or the intervention Group (Group B) based on the pre-generated random number table. As a part of intervention, patients received vitamin E 400mg once daily in addition to the standard of care. The study included newly diagnosed patients with diabetic peripheral neuropathy for a period of initial two months. Patient who already received pregabalin and gabapentin for peripheral

neuropathy, pregnant and lactating females and those unable to comprehend the purpose of the study were excluded. Patients meeting the inclusion criteria were enrolled after obtaining consent of participation for the study. Basic demographic data including age, sex, past history of medications, present drug history was obtained. Laboratory investigations included fasting plasma glucose (FPG), post prandial plasma glucose (PPPG), glycosylated haemoglobin (HBA1C) and serum creatinine.

Efficacy Parameters measured at baseline, 6 months and 12 months included:

- Change in VAS score [13] - The visual analog scale (VAS)scoring instrument is a 100-mm line, oriented horizontally, with the left end indicating "no pain" and the right end representing "very severe pain".
- Change in Mean Pain Score (MPS) - Subjects will be asked to keep a Daily Pain Diary, where they will be required to rate their 24-hour average daily pain intensity perception in a 10-pointer scale.
- Change in BPI-DPN [14] – The Brief Pain Inventory (BPI) assesses the severity of pain (Severity scale), its impact on daily functioning (Interference scale), and other aspects of pain (e.g., location of pain, relief from medications).
- Patient's Global Impression of Change (PGIC) [15] - This questionnaire measures a patient's perception of how treatment has affected their level of activity, symptoms, emotions, and overall quality of life.

Safety parameters included assessment for drug interactions and suspected adverse drug reaction (ADR) monitoring and its subsequent pharmacovigilance work up. Suspected ADRs were assessed for causality using Naranjo [16] and WHO UMC Causality Assessment Scales [17], preventability using Schumock Thornton scale [18] and severity using Hartwig Seigel's Scale [19] respectively. Adherence was assessed using Medication Adherence Rating Scale (MARS) [20]. Quality of Life was assessed using WHO-QoL BREF Questionnaire [21]

Considering changes in the mean visual analogue scoring as the effect, we estimated the standard deviation of control and treatment arm as 17 and 18 respectively, as per literature reports.[22] Calculating for a difference of effect of 10 at 5% level of significance, the estimated sample size was 48 for each arm.

Data collected were statistically analysed. Descriptive data was represented as mean, standard deviation, frequency or percentages. Where possible, continuous and categorical variables were analysed with tests like student's t tests and chi square tests whichever found applicable. A p value of less than 0.05 was considered significant. All statistical measures were analysed using standard statistical software like SPSS V.21.0 and Microsoft Excel.

## Results

The study included a total of 100 patients, 50 patients in each Group. Mean age of the study population was 54.8 years, with gender ratio of 1.8:1 (male: female). Baseline patient characteristics were noted as in Table 1. No significant differences in patient characteristics in terms of age, gender and comorbidities were noted for both groups. As a part of standard of care, all patients received glimepiride, metformin and teneligliptin for their diabetic care.

Mean glycaemic measures like FPG, PPPG, HbA1c and Serum creatinine was assessed. Significantly higher decrease of glycaemic measures was noted for Group B compared to Group A in terms of PPPG and serum creatinine, where a mean decrease of 114.76mg/dl and 0.032mg/dl was noted for Group B as against 103.7mg/dl and 0.048 mg/dl for Group A respectively. However, there was comparable change in HbA1c and FPG for both Groups. (Table 2)

Efficacy measures included assessment of VAS, MPS, BPI and PGIC. There was comparable significant reduction in mean VAS scoring at 6 and 12 months for Group B. Considering all the efficacy measures, there was highest reduction for the pain interference in the intervention arm (Group B), in comparison to Group A. ($p<0.001$). There was non-significant comparable improvement of patients' impression of change for both arms. (Table 3)

Quality of life measures was assessed using WHO QoL BREF questionnaire. (Table 4) Domains of WHO QoL BREF namely physical health, psychological health, social relationship and environmental health

– each showed comparable increased in indices for treatment group B as compared to A, over the time points. Mean treatment adherence scoring significantly increased for treatment group B as compared to A at both 6 months and 12 months of study assessments. (Table 4)

No major safety concerns were reported during the study period. Gastric disturbances like constipation and diarrhoea were observed in 3 cases in Group A and 2 cases in Group B. Causality assessment of the reported reactions using Naranjo and WHO-UMC Algorithm suggested the cases to be under 'possible' grade, while severity of the reported ADRs were 'mild' necessitating no change of treatment. The reactions were non-preventable, and were self-resolved. No drug interactions were noted in our study.

**Illustrations**

**Table 1: Patient Characteristics**

| | | Group A | Group B | Inter Group Difference (p value) |
|---|---|---|---|---|
| Age [Mean ± SD (range)] | | 55.38 ± 11.85 (36.0 – 72.0) | 54.24 ± 11.04 (35.0 – 72.0) | 0.6198 |
| Gender [n (%)] | Male | 32 (64) | 33 (66) | 0.839 |
| | Female | 18 (36) | 17 (34) | |
| Comorbidities [n (%)] | Hypertension | 15 (30) | 17 (34) | 0.67 |
| | Asthma | 5 (10) | 3 (6) | 0.46 |

**Table 2: Glycaemic Measures**

| | | Group A | Group B | Inter Group Difference (p value) |
|---|---|---|---|---|
| FPG | Baseline | 179.64 (15.42) | 185.72 (17.25) | 0.066 |
| | 6 months | 118.86 (12.38) | 125.62 (13.51) | 0.011 |
| | 12 months | 88.78 (7.60) | 93.82 (7.47) | 0.001 |
| PPPG | Baseline | 242.00 (29.15) | 251.42 (25.05) | 0.086 |
| | 6 months | 173.44 (15.10) | 168.84 (15.91) | 0.141 |
| | 12 months | 138.30 (12.88) | 136.66 (11.17) | 0.498 |
| Serum Creatinine | Baseline | 0.78 (0.14) | 0.79 (0.13) | 0.941 |
| | 6 months | 0.76 (0.21) | 0.77 (0.21) | 0.708 |
| | 12 months | 0.74 (0.16) | 0.75 (0.16) | 0.579 |
| HbA1C | Baseline | 8.20 (0.72) | 8.23 (0.76) | 0.820 |
| | 12 months | 6.08 (0.58) | 6.01 (0.60) | 0.555 |

Note: Measures expressed as Mean (SD).

**Table 3: Efficacy Measures**

| | | Group A | Group B | Inter Group Difference (p value) |
|---|---|---|---|---|
| VAS | Baseline | 91.50 (8.59) | 89.90 (10.08) | 0.395 |
| | 6 months | 70.10 (5.30) | 68.40 (10.12) | 0.295 |
| | 12 months | 51.50 (6.25) | 49.20 (6.34) | 0.071 |
| MPS | Baseline | 9.66 (0.48) | 9.60 (0.49) | 0.539 |
| | 6 months | 7.16 (0.37) | 6.90 (1.13) | 0.125 |
| | 12 months | 5.42 (0.76) | 5.82 (1.40) | 0.078 |
| BPI Pain Severity Index | Baseline | 9.52 (0.43) | 9.50 (0.46) | 0.822 |
| | 6 months | 7.12 (0.39) | 6.90 (1.13) | 0.196 |
| | 12 months | 5.45 (0.78) | 4.59 (2.16) | 0.009 |
| BPI Pain Interference Index | Baseline | 9.43 (0.42) | 9.47 (0.40) | 0.576 |
| | 6 months | 7.18 (0.39) | 6.47 (1.07) | 0.000 |
| | 12 months | 6.01 (0.42) | 4.69 (1.80) | 0.000 |
| PGIC | 6 months | 3.66 (0.66) | 3.74 (0.75) | 0.572 |
| | 12 months | 3.84 (0.58) | 3.94 (0.55) | 0.380 |

Note: Measures expressed as Mean (SD).

**Table 4: Quality of Life and Adherence measures**

| | | Group A | Group B | Inter Group Difference (p value) |
|---|---|---|---|---|
| **WHO QoL BREF** | | | | |
| Physical Health | Baseline | 43.62 (13.57) | 48.32 (2.72) | 0.018 |
| | 6 months | 41.00 (3.03) | 62.24 (4.56) | 0.000 |
| | 12 months | 36.72 (20.65) | 62.24 (4.56) | 0.000 |
| Psychological Health | Baseline | 45.56 (2.66) | 52.94 (2.18) | 0.020 |
| | 6 months | 51.68 (5.00) | 88.78 (5.66) | 0.000 |
| | 12 months | 51.68 (5.00) | 92.62 (8.08) | 0.000 |
| Social Relation-ships | Baseline | 40.12 (16.39) | 41.02 (8.91) | 0.734 |
| | 6 months | 47.00 (15.55) | 73.68 (2.51) | 0.000 |
| | 12 months | 48.82 (16.30) | 79.20 (2.78) | 0.000 |
| Environmental Health | Baseline | 42.06 (9.22) | 45.58 (13.08) | 0.123 |
| | 6 months | 47.00 (9.42) | 78.60 (4.85) | 0.000 |
| | 12 months | 50.26 (11.92) | 82.10 (7.29) | 0.000 |
| **Adherence** | | | | |
| MARS Scoring | 6 months | 6.9 (0.78) | 7.25 (0.94) | 0.045 |
| | 12 months | 7.1 (0.83) | 7.60 (0.66) | 0.001 |

Note: Measures expressed as Mean (SD).

## Discussion

Our study noted that addition of vitamin E as an added supplementation to the standard of care showed benefits in terms of patient reported reduced pain interference and pain perception, which also significantly improved overall quality of life in these patients. Some studies have investigated the use of vitamin E in managing DPN symptoms, but the evidence regarding its effectiveness is limited and inconclusive. While the exact mechanism is not fully understood, several potential mechanisms have been proposed. Vitamin E acts as an antioxidant by neutralizing free radicals, which are highly reactive molecules that can damage cells and tissues. Diabetes is associated with increased production of free radicals, leading to oxidative stress. By reducing oxidative stress, vitamin E may help protect nerves from damage and prevent or slow down the progression of DPN. Vitamin E has been shown to have anti-inflammatory properties, which may help reduce inflammation in nerve tissues and alleviate neuropathic symptoms. Diabetes can impair blood flow to peripheral nerves, leading to nerve damage. Vitamin E has been suggested to improve blood flow by enhancing vasodilation and reducing the formation of blood clots. By improving blood flow to nerves, vitamin E may further help to maintain their health and function. [23]

Some studies have reported positive benefits of vitamin E supplementation in DPN, such as reduced pain and improved nerve function.[24] However, other studies have shown no significant effects or mixed results. For example, a randomized controlled trial [25] published in Diabetes Care in 1998 found that high-dose vitamin E supplementation (1,800 IU per day) for one year resulted in modest improvements in nerve conduction velocity and subjective symptoms in individuals with DPN. However, it is worth noting that this study had a relatively small sample size and limitations. On the other hand, a larger clinical trial published in the JAMA Neurology in 2018 found no significant benefit of oral mixed tocotrienols in DPN subjects. [26] It is important to note that high doses of vitamin E can have potential risks, including an increased risk of bleeding, especially in individuals taking blood-thinning medications or with certain medical conditions. Therefore, it is crucial to consult with a healthcare professional before starting any new supplement, including vitamin E, for managing DPN.

However, the present study is constrained by its limited sample size and regional interpretation, which challenges its external generalizability. Also, the study may have been limited by its design issues in not being a double-blind placebo controlled one. Future studies should overcome these limitations. Overall, the evidence regarding the effectiveness of vitamin E in DPN is inconclusive. While some studies have suggested potential benefits, others have shown no significant effects. As with any treatment, it is advisable to discuss options with a healthcare professional who can provide personalized advice and guidance based on individual circumstances. Additionally, focusing on optimal blood sugar control, proper foot care, and other recommended treatments for DPN management should be a priority.

## Conclusion

Our study noted that addition of vitamin E as an added supplementation to the standard of care showed benefits in terms of patient reported reduced pain interference and pain perception, which also significantly improved overall quality of life in these patients. Future research should further focus on this modality in wide subset of subjects.

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**Conflict of Interest:** None Declared

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