Research Article

Vitamin E improves quality of life in patients with alcoholic liver disease

Bhanu Prakash Kolasani, Prasanand Sasidharan, Divyashanthi C M, Adithiya Kumar

Department of Pharmacology, Vinayaka Missions Medical College and Hospital, Vinayaka Missions University, Karaikal, Puducherry, India.

Correspondence to: Bhanu Prakash Kolasani, E-mail: kolasanibhanu@yahoo.co.in

Received January 27, 2016. Accepted March 5, 2016

Introduction

The harmful use of alcohol stands among top five risk factors for disease, disability, and death throughout the world.[1,2] It is a causal factor in more than 200 types of diseases and injury conditions in humans.[3] Although alcohol causes multiple organ damage, liver is the primary organ to be affected as it is involved in metabolism of alcohol. Alcoholic liver disease (ALD) is the third most common cause of chronic liver disease, and, worldwide, alcohol-attributable liver cirrhosis was accountable for 493,300 deaths in 2010.[4] The number of alcohol-related deaths remains high at 2.5 million deaths yearly, constituting 4% of all deaths globally,[5] and demise from ALD constitute roughly 25% of deaths owing to alcohol consumption.[6]

ALD is not only a major cause of morbidity and mortality but also causes a profound effect on quality of life as patients with ALD experience fatigue, loss of self-esteem, work-related problems, anxiety, and depression.[7,8] Assessment of subjective parameters such as quality of life are equally important compared with the objective parameters such as liver function tests but usually neglected in many studies which evaluated various treatment options in ALD. Studies on alcohol-dependent patients have found quality of life as greatly diminished, but little information is available on how quality of life alters following a therapeutic intervention.[9–12]

The evidence that oxidative stress is involved in the pathogenesis of ALD[13] and vitamin E deficiency is being well-documented in patients of ALD.[14,15] It was thought that an antioxidant such as vitamin E could likely be beneficial in patients with ALD. Hence, this study was aimed to evaluate whether vitamin E supplementation will improve the quality of life in patients with ALD.

Access this article online	
Website: http://www.njppp.com	Quick Response Code:
DOI: 10.5455/njppp.2016.6.27012016125	

Materials and Methods

Study Design

The study is a single-center, randomized, open, parallel group, comparative clinical study with an allocation ratio of 1:1.

Place and Duration of Study

The study took place at Department of Medicine in a tertiary-care teaching hospital that was located in a coastal town of South India from May 2014 to August 2014 (i.e., for a period of 12 weeks).

Inclusion Criteria

Patients who are stable and conscious, above 18 years of age, of either sex who met the clinical and biochemical criteria of severe alcoholic hepatitis characterized by a history of chronic and heavy alcohol intake ($>$ 80 g/d for the previous 5 years), rapid onset of jaundice in the absence of a biliary tract obstruction, painful hepatomegaly and ascites, transaminases $\geqslant$ two times above the normal value, an aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio $\geqslant$ 2, neutrophilia, and a total bilirubin $>$ 5 mg/dL admitted in the Department of Medicine were included in this study.

Exclusion Criteria

Patients who did not abstain from alcohol consumption and those who did not consent for the treatment prescribed were excluded. Patients with renal pathology/failure, lung or any

other organ disease, severe hypertension, malignancy, sepsis, bleeding diathesis, and poor prognostic factor were excluded from this study. Pregnant and lactating patients were excluded from this study.

Ethical Considerations

A written informed consent to participate in the study was obtained from all the patients. The study protocol confirmed to the ethical guidelines of the 1975 Declaration of Helsinki, and ethical clearance was obtained from Institutional Ethical Committee before commencing the study. All the patients were included in the study after explaining the patient's diagnosis, the nature and purpose of the proposed treatment, the risks and benefits of the proposed treatment, alternative treatment, and the risks and benefits of the alternative treatment.

Sample Size, Sample Grouping, and Drug Administration

After assessment for eligibility criteria, a total of 30 patients were selected for the study and randomized into two groups of 15 each. Randomization was done by using computer generated random list. First group designated as Group-A received the standard treatment for ALD, and the second group designated as Group-B received vitamin E as capsule (one capsule—twice daily) along with the standard treatment. The standard treatment for the patients with ALD in our institute includes hepatoprotective drugs such as ursodeoxycholic acid or Liv 52 or both together, a diuretic such as spironolactone or furosemide for treating ascites, a corticosteroid such as prednisolone, an antibiotic such as cephalosporin or metronidazole, an antiulcer drug such as pantoprazole or ranitidine, an IV fluid such as 25% dextrose or Ringer's Lactate, a vitamin preparation such as B complex or vitamin K, drugs such as lactulose or l-ornithine l-aspartate for prevention/treatment of hepatic encephalopathy, a beta blocker such as propranolol for prevention/treatment of variceal bleeding, and chlordiazepoxide for treating symptoms of alcohol withdrawal. Vitamin-E (Evion—400 IU) capsules were used for this study. All the patients included in this study were requested to abstain from alcohol consumption.

Primary and Secondary Outcome Measure

The primary outcome measure was the improvement in the quality of life scores in various domains of Chronic Liver Disease Questionnaire (CLDQ) assessed at the time of admission as a baseline measure and 12 weeks after the intervention. Secondary outcome measure was the percentage change in various domain scores of CLDQ before and after the intervention.

Patient's details were collected and verified. Their present clinical severity and features of alcohol-induced liver disease were noted. The following demographic details of age, sex, present condition and history, and duration of alcohol consumption were obtained, and presence of comorbid factors such as hypertension, diabetes, cerebrovascular disease, coronary artery disease, peptic ulcer disease, and chronic pulmonary disease were noted. The body mass index, body temperature, blood pressure, heart rate, and respiratory rate were recorded for all the patients. Details of clinical examination were duly noted down. Use of concurrent allopathic and alternative medications for other systemic issues were noted and excluded based on their reported interactions. Patient's clinical data were maintained confidentially.

Quality of life in these patients was assessed at the time of admission and 12 weeks after the treatment using CLDQ.[16] CLDQ has a total of 29 questions, which are categorized into 6 domains as follows:

Abdominal symptoms (AS): Questions 1, 5, 17.

Fatigue (FA): Questions 2, 4, 8, 11, 13.

Systemic symptoms (SY): Questions 3, 6, 21, 23, 27.

Activity (AC): Questions 7, 9, 14.

Emotional function (EF): Questions 10, 12, 15, 16, 19, 20, 24, 26.

Worry (WO): Questions 18, 22, 25, 28, 29.

Each question has seven response options. The response options ranging from one to seven are based on the ascending period of time the patient experiences the problem as asked in the question. Hence, option one is least period of suffering, and option seven is the maximum period of suffering.

Response under each domain is summed up, and average value is taken by dividing the sum with number of questions under that domain. Then, each domain is summed up, and global CLDQ value is obtained.

Statistical Analysis

Data collected under each group were summarized as mean ± SD. Statistical analysis was carried out using paired *t*-test for within the group comparisons and unpaired *t*-test for between the group comparisons. A "*P*" value of <0.001 is considered statistically highly significant, whereas a "*P*" value of <0.05 is considered as statistically significant, and a "*P*" value of >0.05 was considered statistically not significant. The IBM–SPSS software, version 21.0 software was used for statistical analysis of data.

Result

A total of 41 patients with ALD were assessed for eligibility, of which 30 patients were selected based on inclusion and exclusion criteria and their willingness to participate in the study. Three patients did not meet the inclusion/exclusion criteria, whereas eight patients declined to participate in the study. The remaining 30 patients were randomized into two groups of fifteen each and designated as Group A (received standard treatment) and Group B (received standard treatment and vitamin E). One patient was lost during the follow-up in Group B, and 29 patients [15 in Group A and 14 in Group B] were followed up after the treatment duration of 12 weeks. Figure 1 shows the flow of participants of this study through its various phases.

The two groups were homogenous with respect to most of the baseline demographic data, including patient's age, duration of alcohol consumption, and various CLDQ scores except for CLDQ-FA and CLDQ- SY domain scores [Table 1].

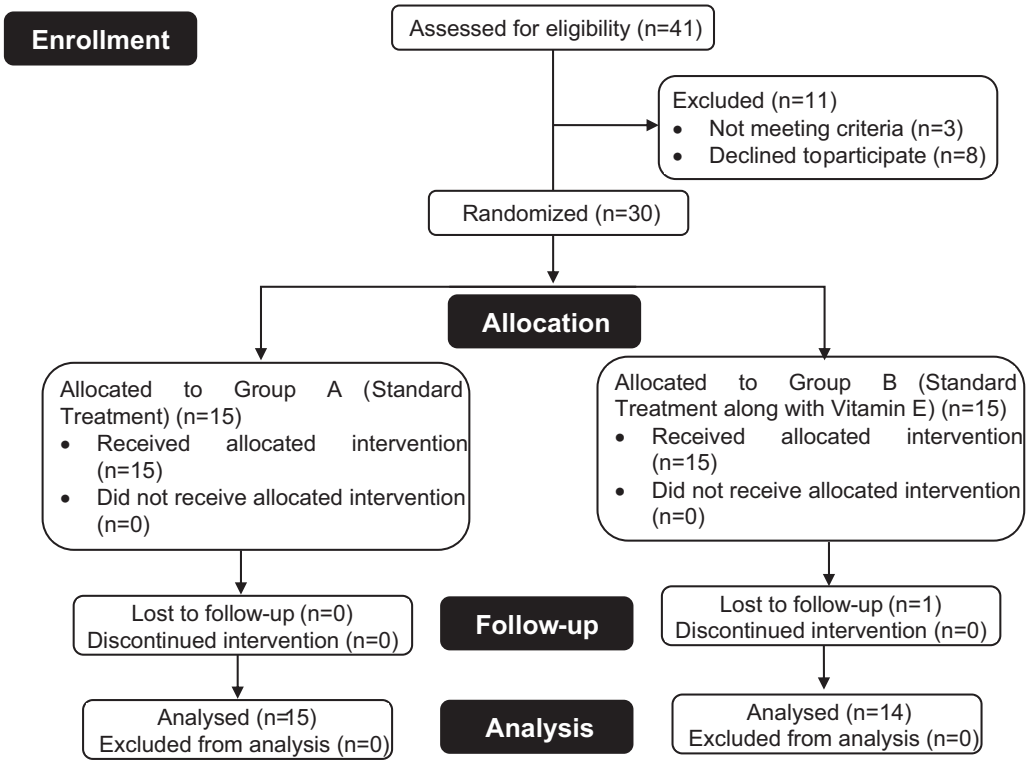

Figure 1: Consort flow diagram of patients of the study through its various phases.

In Group A, scores in CLDQ-FA, CLDQ-AC domains, and CLDQ-Global showed a statistically highly significant ($P < 0.001$) improvement, whereas those in CLDQ- AB, CLDQ-EM, and CLDQ-WO domains showed only a significant ($P < 0.05$) improvement. CLDQ-SY domain score improved, but it was not statistically significant ($P > 0.05$) [Table 2].

In Group B, there was a statistically highly significant change in all the domains of CLDQ and CLDQ-Global score after the treatment duration compared with their baseline values [Table 3].

In group A, within the various domains of CLDQ, the highest change was observed in CLDQ-AC (186.89%), followed by

Table 1: Baseline demographic data and CLDQ scores of the patients

Parameters	Baseline parameters (before the treatment) mean ± SD		*P*
	Group A (standard treatment)	Group B (vitamin E with standard treatment)	
Age	43.93 ± 6.78	40.47 ± 6.71	0.170*
Years of alcohol consumption	17.20 ± 8.14	18.13 ± 6.80	0.736*
CLDQ-AB (abdomen)	2.76 ± 1.65	2.39 ± 1.46	0.518*
CLDQ-FA (fatigue)	2.61 ± 1.28	1.61 ± 0.79	0.016†
CLDQ-SY (systemic)	4.04 ± 1.13	3.09 ± 0.95	0.019 †
CLDQ-AC (activity)	2.06 ± 1.12	2.17 ± 1.86	0.840*
CLDQ-EM (emotion)	3.36 ± 1.45	3.25 ± 0.94	0.810*
CLDQ-WO (worry)	3.71 ± 1.31	3.96 ± 0.93	0.546*
CLDQ-GLOBAL	3.09 ± 1.07	2.75 ± 0.50	0.098*

CLDQ: Chronic Liver Disease Questionnaire (CLDQ).
All the values are given as mean ± standard deviation.
Δ, difference; * *P* value is statistically not significant (⩾0.05); †*P* value is statistically significant (<0.05); ‡*P* value is statistically highly significant (<0.001).

Table 2: Student paired t-test results for within the group comparison of Group A

Parameters	Group A (standard treatment)		*P*
	Before the treatment (mean ± SD)	After the treatment (mean ± SD)	
CLDQ-AB (abdomen)	2.76 ± 1.65	4.13 ± 1.61	0.011†
CLDQ-FA (fatigue)	2.61 ± 1.28	4.44 ± 1.42	<0.001‡
CLDQ-SY (systemic)	4.04 ± 1.13	4.60 ± 1.33	0.189*
CLDQ-AC (activity)	2.06 ± 1.12	4.75 ± 1.53	<0.001‡
CLDQ-EM (emotion)	3.36 ± 1.45	4.81 ± 1.14	0.003†
CLDQ-WO (worry)	3.71 ± 1.31	5.29 ± 1.06	0.001†
CLDQ-GLOBAL	3.09 ± 1.07	4.67 ± 1.01	<0.001‡

CLDQ: Chronic Liver Disease Questionnaire (CLDQ).
All the values are given as mean ± standard deviation.
Δ, difference; **P* value is statistically not significant (⩾0.05); †*P* value is statistically significant (<0.05); ‡*P* value is statistically highly significant (<0.001).

CLDQ-FA (111.70%) and CLDQ-AB (83.23%). The least change was observed in CLDQ-SY (23.63%). In group B, the highest change was observed in CLDQ-FA (342.91%), followed by CLDQ-AC (328.55%) and CLDQ-AB (223.53%). The least change was observed in CLDQ-WO (73.17%) [Figure 2].

When the differences observed in various domains of CLDQ scores in Group A were compared with those seen in Group B by using independent *t*-test, the changes in CLDQ-Global score and CLDQ-SY domain score observed in Group B were highly significant ($P < 0.001$); the changes observed in the CLDQ-AB and CLDQ- FA domain scores were significant ($P < 0.05$), whereas the changes observed in CLDQ-AC, CLDQ-EM, and CLDQ- WO domain scores were not statistically significant ($P > 0.05$) compared with their respective changes observed in Group A [Table 4].

Discussion

To the best of our knowledge, there is no study evaluating the efficacy of vitamin E supplementation on quality of life in patients with ALD. Our study for the first time assessed the quality of life in these patients using CLDQ. Usually, the quality of life aspect of the disease is neglected, but it is as important as other aspects of the disease.

ALD remains a major health problem not only in India but also worldwide. In spite of important progresses in the knowledge of the pathogenesis of alcohol-related liver injury and many drugs such as corticosteroids and pentoxifylline being used in this condition, until now, there are no FDA-approved treatments for ALD, and, so, the search for effective and safe drugs is continuing.

Both the groups were homogenous in their baseline demographic data and in most of the CLDQ scores, which indicate that the two groups were properly randomized [Table 1]. Even though there are several studies demonstrating that women develop liver disease after exposure to lower quantities of alcohol and over shorter time periods,[17,18] in our study, all the 30 patients who were included in the study were male subjects. This may be owing to sociocultural aspects of our country, where almost exclusively male subjects are involved in

Table 3: Student paired t-test results for within the group comparison of Group B

Parameters	Group B (vitamin E with standard treatment)		*P*
	Before the treatment (mean ± SD)	After the treatment (mean ± SD)	
CLDQ-AB (abdomen)	2.49 ± 1.46	6.30 ± 0.38	<0.001‡
CLDQ-FA (fatigue)	1.66 ± 0.80	6.16 ± 0.56	<0.001‡
CLDQ-SY (systemic)	3.13 ± 0.98	6.36 ± 0.49	<0.001‡
CLDQ-AC (activity)	2.26 ± 1.90	6.12 ± 0.54	<0.001‡
CLDQ-EM (emotion)	3.32 ± 0.93	6.20 ± 0.50	<0.001‡
CLDQ-WO (worry)	3.90 ± 0.93	6.39 ± 0.43	<0.001‡
CLDQ-GLOBAL	2.79 ± 0.49	6.25 ± 0.28	<0.001‡

CLDQ: Chronic Liver Disease Questionnaire (CLDQ).
All the values are given as mean ± standard deviation.
Δ, difference; * *P* value is statistically not significant (⩾0.05); †*P* value is statistically significant (<0.05); ‡*P* value is statistically highly significant (<0.001).

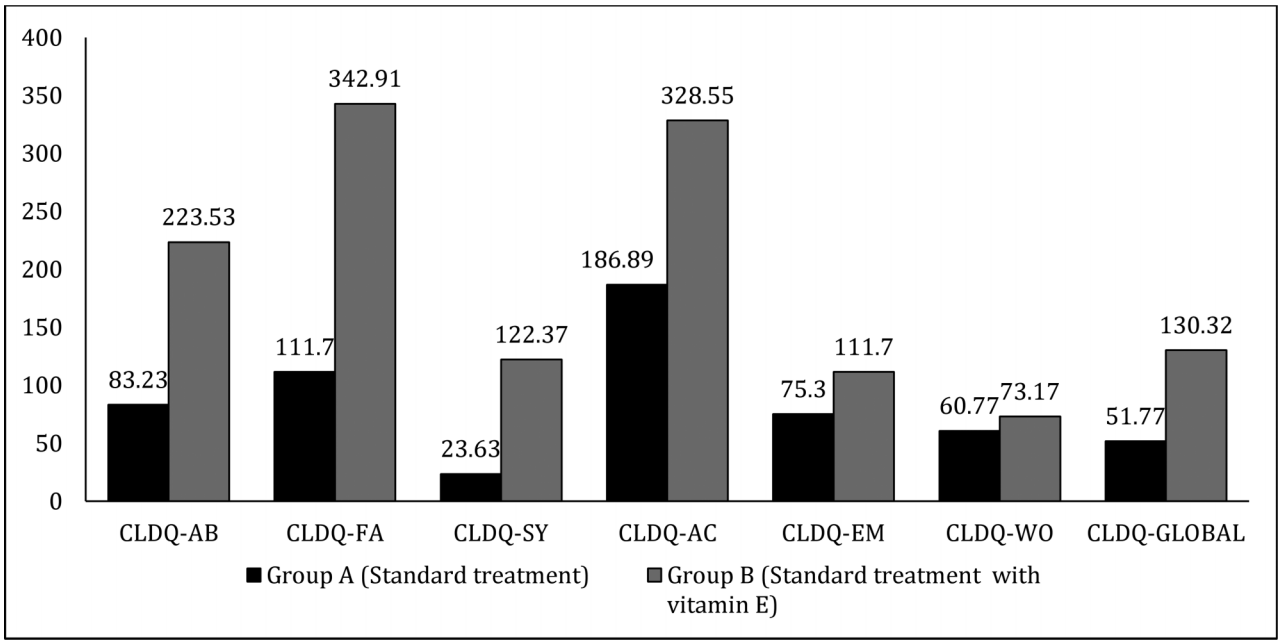

Figure 2: Mean percentage change observed in both the groups for CLDQ scoring. CLDQ-AB, abdomen; CLDQ-FA, fatigue; CLDQ-SY, systemic; CLDQ-AC, activity; CLDQ-EM, emotion; CLDQ-WO, worry.

alcohol intake. Moreover, we observe that, at a very early age only, people of this region are exhibiting ALD. This may be ascribed to the habit of consuming the alcohol from a very early age compared with other parts of the country. Moreover, our hospital is located in Karaikal, which is a part of Pondicherry, a union territory, where the reduced cost of alcoholic beverages owing to the reduced tax compared with other parts of our country, also is contributing here to the increased prevalence of alcoholism and subsequently ALD in this region.

A highly significant improvement in some of the domains of CLDQ scores and in CLDQ-Global score in Group A indicates that standard treatment has to an extent improved the quality of life in these patients.

There was a statistically highly significant change in all the domains of CLDQ and CLDQ-Global score in Group B, which indicates a very good improvement in the quality of life in ALD patients when Vitamin E was added. No other study previously has assessed the quality of life in ALD patients.

Table 4: Independent t-test results for comparison of differences in both the groups

Parameters	Mean percentage change (mean ± SD)		*P*
	Group A (Standard Treatment)	Group B (vitamin E with standard treatment)	
CLDQ-AB (abdomen)	83.23 ± 101.01	223.53 ± 145.27	0.006†
CLDQ-FA (fatigue)	111.70 ± 135.65	342.91 ± 175.77	0.001†
CLDQ-SY (systemic)	23.63 ± 55.34	122.37 ± 71.66	<0.001‡
CLDQ-AC (activity)	186.89 ± 163.06	328.55 ± 214.83	0.058*
CLDQ-EM (emotion)	75.30 ± 93.85	111.70 ± 118.16	0.369*
CLDQ-WO (worry)	60.77 ± 62.81	73.17 ± 46.12	0.548*
CLDQ-GLOBAL	51.77 ± 53.33	130.32 ± 41.18	<0.001‡

CLDQ: Chronic Liver Disease Questionnaire (CLDQ).
All the values are given as mean ± standard deviation.
Δ, difference; * *P* value is statistically not significant (⩾0.05); †*P* value is statistically significant (<0.05); ‡*P* value is statistically highly significant (<0.001).

When the differences observed in various parameters in Group A were compared with those seen in Group B, the changes in CLDQ-Global score and CLDQ-SY domain score observed in Group B were highly significant ($P < 0.001$), and CLDQ-AB domain and CLDQ-FA domain in Group B were statistically significant ($P < 0.05$) compared with their respective changes observed in Group A [Table 4], which indicates that addition of vitamin E in Group B has improved the quality of life. In a previous study with vitamin E alone in ALD patients, it showed little benefit which might be owing to an inadequate dose of 500 mg per day[19] used in that study. In our study, we have used a recommended and an adequate dose of vitamin E of 800 mg per day.

As mentioned earlier, oxidative stress plays a key role in the pathogenesis of ALD. Alcohol metabolism results in increased synthesis of NADH and suppression of mitochondrial β oxidation and increased lipid peroxidation in liver. This liberates oxygen-free radicals and decrease in mitochondrial glutathione and S-adenosyl-L-Methionine levels, thus depleting the endogenous antioxidant capabilities.[13,20,21] Vitamin E, being an antioxidant, is expected to be useful in patients with ALD because it has experimentally (in rats) proven hepatoprotective capabilities including membrane stabilization, reduced NF-kB activation and tumor necrosis factor production, and inhibition of hepatic stellate cell activation.[22–24] The beneficial effect of improving the quality of life in this study might be explained by the abovementioned antioxidant properties of Vitamin E.

The limitations of this study are its small sample size, which can be owing to reluctance of patients to get admitted, and even many of the admitted patients were not willing to participate in the study. A larger study involving more number of patients can be done to obtain better results. Because of logical constraints, this study was conducted as an open-labeled study. A blinded study would have decreased the bias and would have yielded a more accurate result.

Conclusion

In conclusion, supplementation of vitamin E to standard treatment has significantly improved the quality of life in patients with ALD as evidenced by an improvement in the CLDQ scoring. As this study was done at our hospital with relatively less number of patients, the findings of this study must be confirmed by conducting multicentric studies involving larger number of patients.

Acknowledgments

We extend our heartfelt thanks to Dr. Sakthivel, Professor and HOD, Department of Medicine, for his cooperation in the smooth conduction of this study.

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How to cite this article: Kolasani BP, Sasidharan P, Divyashanthi CM., Kumar A. Vitamin E improves quality of life in patients with alcoholic liver disease. Natl J Physiol Pharm Pharmacol 2016;6: 269–275

Source of Support: Nil, **Conflict of Interest:** None declared.