Vitamin E Use Is Associated with Improved Survival in an Alzheimer's Disease Cohort

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Key Words

Alzheimer's disease • Survival • Vitamin E

Abstract

Background: Vitamin E at a dose of 2,000 IU per day has been shown to delay Alzheimer's disease (AD) progression, but recent studies have questioned the safety of this dose level and the overall efficacy of vitamin E in AD treatment.

Methods: We analyzed the survival history of 847 probable or mixed AD patients followed in a research center between 1990 and the censoring date of December 31, 2004. Standard practice during this period was to recommend vitamin E at 1,000 IU twice daily to all patients. We used Cox proportional hazards modeling to assess the association of vitamin E alone, or in combination with a cholinesterase inhibitor (ChEI), with all-cause mortality, adjusting for important covariates. Approximately two thirds of the patients took vitamin E with a ChEI, 10% took vitamin E alone, and 15% took no antimental drug. **Results:** The adjusted hazard ratio (HR) associated with vitamin E (with or without a ChEI) was 0.71 (95% CI: 0.57–0.89; $p = 0.003$). Compared to the no drug treatment group, the HR for vitamin E alone or with another drug was 0.77 (95% CI: 0.60–1.0); the HR for ChEI use alone was 1.2 (95% CI: 0.87–1.60). **Conclusion:** The results do not support a concern over increased mortality with high-dose vitamin E supplementation.

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Background

Vitamin E (α -tocopherol) is a lipid-soluble vitamin with antioxidant properties which may decrease free-radical-mediated damage in neuronal cells. Many, but not all, observational studies have suggested a protective effect of vitamin E with or without other antioxidant vitamins for the prevention of cognitive decline and Alzheimer's disease (AD) [1–5]. Because of both laboratory- and population-based data, vitamin E has been proposed as a treatment to delay neurodegeneration in AD patients. One randomized clinical trial in moderately severe AD patients resulted in a significant delay in disease progression (death, institutionalization, loss of activities of daily living, and Clinical Dementia Rating score increase) in patients assigned 2,000 IU/day of vitamin E compared to placebo [6]. However, a trial of 2,000 IU of vitamin E daily had no effect on delaying the progression of AD in participants with amnesic mild cognitive impairment [7]. Recent meta-analyses of randomized trials involving vitamin E in cardiac patients and other patient groups suggest a slightly higher mortality risk associated with vitamin E treatment [8–10]. One meta-analysis [9] concluded that the mortality rate associated with vitamin E treatment increased in a nonlinear dose-dependent manner, with the relative risk beginning to rise above 1 at doses ≥ 400 IU/day.

The AD and Memory Disorders Center (ADMDC) at the Baylor College of Medicine, Houston, Tex., USA, has served as a referral center for AD diagnosis and treatment for over 20 years. Between 1992 and 2004, standard practice in the Baylor ADMDC was to recommend vitamin E supplementation at a dose of 1,000 IU 2 times per day to all AD patients, in addition to any other indicated antedementia drugs. Prior to 1992, some patients self-supplemented themselves, although usually at lower doses than 2,000 IU/day. After 2004, patients continued to receive this recommendation and were given an information sheet summarizing the potential benefits and risks reported in the literature. The purpose of this study was to determine if treatment with vitamin E was associated with higher mortality in the Baylor ADMDC AD cohort.

Patients and Methods

Subjects

Patients were eligible for the study if they had agreed to have their clinical data stored in a database approved by the institutional review board at the Baylor College of Medicine, met the criteria for a diagnosis of probable AD based on the NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association) [11], and had at least 1 complete comprehensive annual follow-up evaluation after their initial visit. Patients who presented with significant strokes at baseline or met criteria for probable ischemic vascular dementia (NINDS-AIREN, National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences) were excluded, even if AD was suspected. However, patients who met NINCDS criteria for probable AD but had cerebrovascular changes (extensive white matter disease or lacunae in noncortical regions), or who developed a stroke after the probable AD diagnosis, were included in order to examine the impact of concomitant cardiovascular disease (CVD) on survival. All patients underwent an evaluation by a neurologist and completed a standardized dementia workup that has been in continuous use since 1989 [12]. The analysis included all patients in the cohort who met the eligibility criteria through the censoring date of December 31, 2004.

Measures

The initial visit included a detailed history and interview with the patient and informant, neurological and physical examinations, a neuroimaging study of the brain, neuropsychological testing and screening laboratory studies. The duration of illness was estimated by the physician at the new patient's visit by a standardized procedure reported to the nearest half-year [13]. The initial battery of neuropsychological tests, along with a neurological and physical exam, were repeated annually.

Drugs approved for the treatment of AD first became available in the USA in 1993. The first class of drugs developed for AD consisted of the cholinesterase inhibitors (ChEI) including tacrine

(no longer available due to side effects), galantamine, rivastigmine and donepezil. Memantine, a drug that modulates glutamate via N-methyl-D-aspartate receptor antagonism, was approved in 2003 for the treatment of moderate-to-severe AD. Since 1992, the Baylor ADMDC has recommended the use of vitamin E as a supplement to other antedementia treatment or alone if other treatments are contraindicated. At each visit, the patient's medication history during the interval between visits, including his or her vitamin E use, was recorded on a standardized form and stored in the electronic data base.

Baseline neuropsychological testing included the MMSE (Mini-Mental State Examination) [14], a widely used dementia severity test with scores that range from 0 to 30 points. The description of the full battery of neuropsychological tests used in the ADMDC cohort has been described elsewhere [12].

The vital status of each actively followed patient was updated every 6 months by telephone follow-up and searches of the National Death Index.

Analysis

Medication exposure during the interval between each patient's visits was represented with indicator variables representing the classes of medications taken by the patient. Thus, for example, any ChEI use since the last visit was coded as 1, and 0 otherwise. For the survival analysis, a single variable, representing mutually exclusive exposure categories in each interval, was created to reflect the following combinations: no drug use (reference category), vitamin E alone or with another antedementia drug, and ChEI without vitamin E. After 2003, some regimens included memantine. Between 2003 and 2004, the number of patients taking memantine alone was too small to be analyzed as a separate group. Approximately 5% of the patients classified as taking vitamin E with or without a ChEI during this period could also have taken memantine.

Time-dependent Cox survival models were constructed to test the effects of the independent medication exposure variables on survival, adjusting for potential confounders including age at diagnosis, sex, race (white or nonwhite), years of education, duration of symptoms, baseline severity of disease based on MMSE score [14] (20–30 = mild; 10–19 = moderate; 0–9 = severe), and presence of relevant cerebrovascular disease features on imaging.

Two survival models were tested, one in which patients on any regimen that included vitamin E were compared to those not taking vitamin E (including patients taking no antedementia drugs), and one in which 3 groups were compared: (1) patients on antedementia drug regimens that included vitamin E; (2) patients on regimens that did not include vitamin E, and (3) a no drug treatment reference group.

Results

The characteristics of the 847 patients who met the basic inclusion criteria are shown in table 1. The average age at the baseline visit was 73.5 ($\pm$ 8.6) years, and 67.3% of the subjects were female. The severity of the disease at baseline was classified as mild in 52%, moderate in 36%

and severe in 12% of the cases. The average survival from first ADMDC visit to death was 5.5 ± 2.8 years (median survival: 5.0 years). The earliest cohort entry date for the patients included in the analysis was January 2, 1990, and the latest entry date was January 23, 2003.

Drug exposure information on the interval before any given visit could not be determined with certainty in approximately 10% of the visits. Because of the longitudinal nature of the data, the patients with undetermined drug exposure varied from interval to interval. In table 2, we report the distribution of exposure to each defined category of antimentia drugs (including vitamin E) for the first ADMDC visit, the second ADMDC visit (required for inclusion in the cohort) and the last ADMDC visit. At the first ADMDC visit, 54% of the patients for whom drug exposure information was available were not taking any antimentia medication, and just over 25% were taking vitamin E alone or with a ChEI. By the final visit, 62% of the patients were taking both vitamin E and a ChEI, 9% were taking vitamin E alone, 13% were taking a ChEI without vitamin E, and 16% were not taking any drug.

Table 1. Patient characteristics

Age at first ADMDC visit, years	73.5 $\pm$ 8.6	43.2–93.9
Females, n	570 (67.3%)	
Nonhispanic whites, n	741 (87.5%)	
Duration of education, years	13.4 $\pm$ 3.5	0–29
Duration of symptoms, years	3.8 $\pm$ 2.5	0.5–20
Baseline MMSE score	18.8 $\pm$ 6.8	1–30
Baseline severity category, n		
Mild (MMSE $\geq$ 20)	439 (51.8%)	
Moderate (MMSE 10–19)	309 (36.5%)	
Severe (MMSE <10)	99 (11.7%)	
Presence of CVD at baseline, n	49 (5.8%)	
Survival time from first ADMDC visit, years	5.5 $\pm$ 2.8	0.99–14.7

Values denote means $\pm$ SD or ranges (column 3), unless specified otherwise.

In the first Cox survival model (table 3), in which vitamin E use was compared to no vitamin E use, vitamin E use was associated with a 29% reduction in mortality risk (hazard ratio, HR = 0.71; 95% CI: 0.57–0.89; $p = 0.003$) after adjusting for age, sex, race and the baseline severity of symptoms. Neither education nor the duration of symptoms before the baseline visit nor concurrent cerebrovascular disease was significantly associated with survival.

In the model in which no drug treatment served as the reference group for vitamin E use (with or without a ChEI) and ChEI use without vitamin E, there was no survival benefit with ChEI use alone (HR = 1.20; 95% CI: 0.87–1.65; $p = 0.273$), whereas those taking vitamin E with or without a ChEI had a 23% lower mortality risk compared to those not taking any drugs (HR = 0.77; 95% CI: 0.60–1.00; $p = 0.051$).

The survival functions associated with the 3 categories of drug exposure evaluated in model 2 are depicted in figure 1. The survival curves indicate that the survival advantage associated with vitamin E use does not become apparent until after 4 or more years of follow-up.

Discussion

There was no evidence that treatment with high doses of vitamin E had an adverse effect on survival in an AD cohort followed up for up to 15 years. In fact, patients whose regimens included vitamin E tended to survive longer than those taking no drug or a ChEI alone. It is noteworthy that the survival benefit to those taking vitamin E did not become apparent until after 4 or more years of follow-up.

The results of this study do little to resolve the controversies over the benefits and risks of vitamin E supplementation in the prevention or treatment of AD. In spite of significant protective effects seen against cancer, heart disease and dementia in some, but not all, observational studies, randomized clinical trials have generally failed

Table 2. Distribution of drug exposure categories at first, second and last ADMDC visit (n)

	Vitamin E + ChEI	ChEI without vitamin E	Vitamin E alone	No drug treatment	Total with drug exposure recorded	Exposure undetermined	Total patients in cohort
First ADMDC visit	137 (18.5%)	135 (18.2%)	67 (9.1%)	401 (54.2%)	740	104 (12.3%)	847
Second ADMDC visit	428 (57.5%)	121 (16.2%)	53 (7.1%)	143 (19.2%)	745	87 (10.3%)	847
Final ADMDC visit (if >2)	310 (61.9%)	65 (13.0%)	47 (9.4%)	79 (15.8%)	501	50 (9.1%)	552

Fig. 1. Survival functions associated with the 3 categories of drug exposure evaluated in model 2.

to show a benefit in those taking the supplement. The most recent negative result was announced in November 2008, when a large NIH-sponsored prostate cancer prevention trial, the Selenium and Vitamin E Cancer Prevention Trial (SELECT) [15] (<http://www.crab.org/select>), was stopped due to evidence of a lack of benefit with regard to the primary endpoint, accompanied by statistically nonsignificant trends toward harm (e.g. higher incidence of type 2 diabetes), among those treated with 400 IU vitamin E and/or 200 µg selenium per day. The SELECT included a substudy examining the effects of vitamin E and selenium on the prevention of dementia, but no results from that substudy have been announced yet.

The study of vitamin E and selegiline to prevent progression in moderate AD reported by Sano et al. [6] in 1997 remains the only randomized clinical trial that supports both the safety and efficacy of high-dose vitamin E supplementation in AD. The dose of vitamin E tested in this trial was 2,000 IU per day. Of the trials included in the meta-analysis by Miller et al. [9], only one other, in a Parkinson's disease population, tested a dose as high as 2,000 IU per day. The trend toward a dose-related increase in mortality with higher doses of vitamin E led Miller et al. [9] to advise against a supplementation with more than 400 IU per day.

Roberts et al. [16] argued that little was known about dose-dependent effects of vitamin E on the suppression of oxidative stress and conducted a dosing and time course study on individuals with elevated plasma cholesterol. They found that the peak reduction of oxidative stress, as measured by plasma F₂-isoprostane, did not occur until week 16 of the supplementation with 3,200 IU

Table 3. Cox's survival analysis for different exposure categories

	HR	95% CI	p
<i>Vitamin E regimens versus all other categories (n = 764)</i>			
Age	1.03	1.02–1.05	<0.001
Sex (1 = male; 0 = female)	1.90	1.52–2.37	<0.001
Race (1 = white; 0 = other race/ethnicity)	1.81	1.25–2.62	0.002
Baseline severity			
Moderate vs. severe	0.86	0.63–1.19	0.376
Mild vs. severe	0.52	0.37–0.72	<0.001
Vitamin E regimen	0.71	0.57–0.89	0.003
<i>Vitamin E regimens and non-vitamin-E regimens versus no drug</i>			
Age	1.03	1.02–1.05	<0.001
Sex (1 = male; 0 = female)	1.93	1.54–2.42	<0.001
Race (1 = white; 0 = other race/ethnicity)	1.83	1.26–2.65	0.001
Baseline severity			
Moderate vs. severe	0.84	0.61–1.67	0.300
Mild vs. severe	0.50	0.36–0.70	<0.001
Drug regimen			
Vitamin E (alone or with other antedementia drug) vs. no drug	0.77	0.60–1.00	0.051
ChEI without vitamin E vs. no drug	1.20	0.87–1.6	0.273

The duration of symptoms, education and CVD was nonsignificant ($p > 0.20$) in all models (HR not shown).

per day, and that a significant reduction in F₂-isoprostane levels did not occur with doses less than 1,600 IU per day. These authors concluded that the results of both observational and experimental studies on vitamin E effects were difficult to interpret because of the lack of documenta-

tion of the relationship between vitamin E dosage and change in oxidative stress.

Patients in most clinical treatment trials are followed up for less than 5 years. The fact that the survival curves in our AD cohort did not begin to diverge until after 4 years of follow-up raises the possibility that the benefits of vitamin E supplementation are difficult to observe under the constraints of a randomized trial. Another factor that must be considered in evaluating the results is that only 6% of the patients in our AD cohort had features of concurrent cerebrovascular disease, and the population is thus quite different from that included in trials that have evaluated vitamin E supplementation to prevent cardiovascular and cerebrovascular outcomes. We adjusted for the presence of CVD in our analysis, but the number of patients with this feature was too small to be analyzed separately.

The results of our observational study in an AD cohort are not consistent with a harmful effect of vitamin E on overall survival. In light of the potential for beneficial effects and mixed clinical trial evidence, they emphasize

the need for additional research on vitamin E supplementation in AD using a dose range that extends above 400 IU per day.

The strength of our study is that it includes a large number of AD patients followed up over a relatively long period of time with a standardized documentation of medication history and outcomes. In addition, the study reflects the outcomes of actual clinical practice in AD treatment.

The findings of the study must be interpreted with caution in view of its observational nature. The numbers of patients grouped in the different medication exposure categories were not equal, and selection factors associated with long-term drug exposure cannot be ruled out as alternative explanations for the findings.

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