

Phase II Study of Alpha-Tocopherol in Improving the Cognitive Function of Patients with Temporal Lobe Radionecrosis

Agnes S. Chan, Ph.D.¹
 Mei-Chun Cheung, Ph.D.¹
 Stephen C. Law, M.B.B.S.²
 John H. Chan, M.B.B.S.³

¹ Department of Psychology, Chinese University of Hong Kong, Hong Kong SAR, China.

² Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong SAR, China.

³ Department of Medicine, Queen Elizabeth Hospital, Hong Kong SAR, China.

Presented in part at the 55th Annual Meeting of the American Academy of Neurology, Honolulu, Hawaii, March 29–April 5, 2003.

Supported in part by a donation from Cultural Home Limited.

Address for reprints: Agnes S. Chan, Ph.D., Department of Psychology, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong SAR, China; Fax: (011) 852 2603 5019; E-mail: aschan@psy.cuhk.edu.hk

Received July 7, 2003; revision received September 9, 2003; accepted October 1, 2003.

BACKGROUND. Radiotherapy is an important treatment modality for brain tumors and is the standard radical treatment for nasopharyngeal carcinoma (NPC). However, the treatment is not free of side effects, and one possible neurologic sequela is the occurrence of temporal lobe radionecrosis (TLN) associated with cognitive dysfunction. Currently, there is no effective intervention to improve patients' cognitive performance.

METHODS. Twenty-nine patients with TLN after radiotherapy for NPC were recruited on a voluntary basis. Among them, 19 patients (15 males and 4 females) received a megadose of alpha-tocopherol (vitamin E) (2000 international units per day) for 1 year, whereas the other 10 (5 males and 5 females) served as control patients. Their cognitive function (i.e., global cognitive ability, attention, memory, language, and executive function) was evaluated by a battery of neuropsychological tests before and after treatment.

RESULTS. Significant improvement in global cognitive ability ($P = 0.035$) and memory (verbal: $P = 0.036$; visual: $P = 0.007$) occurred among patients in the treatment group after a 1-year medication period. In addition, the executive function of the treatment group improved significantly ($P = 0.04$). No difference was found between the two groups with respect to attention or language.

CONCLUSIONS. The current investigation was a preliminary study on the effect of alpha-tocopherol on the cognitive function of patients with TLN after radiotherapy for NPC. In view of the absence of effective treatment for patients with cerebral radionecrosis, alpha-tocopherol has the potential to be a complementary intervention for patients with cognitive dysfunction due to TLN. *Cancer* 2004;100:398–404. © 2003 American Cancer Society.

KEYWORDS: alpha-tocopherol, nasopharyngeal carcinoma, temporal lobe radionecrosis, neuropsychological function, radiotherapy.

Cognitive dysfunction due to temporal lobe radionecrosis (TLN) is one of the most common cognitive sequelae experienced by patients after radiotherapy for nasopharyngeal carcinoma (NPC).¹ The severity of cognitive impairment depends on the volume of the lesion found in the brain—i.e., the larger the lesion volume, the more severe the memory impairment.² However, there currently is no effective treatment to enhance the cognitive function of patients with NPC who develop TLN after radiotherapy. Although steroids are used to treat the cerebral edema associated with radionecrosis, the treatment may have side effects. Instead of improving the cognitive function of patients with NPC, studies have indicated that the use of corticosteroids can cause a decline in cognitive function, including memory

loss.^{3,4} Some patients even die of uncontrolled sepsis related to induced immunosuppression.⁵

Although the cause of the pathologic change for cerebral radionecrosis is not fully understood, it has been proposed that it may be related to free radical generation and tissue peroxidation in the central nervous system.^{6,7} With the discovery of the negative impacts of free radical generation on brain function, many studies have been conducted to explore the effectiveness of alpha-tocopherol (vitamin E) on brain function. The antioxidative function of vitamin E has been studied extensively in animals and humans over decades. In a neurobiologic experiment with hypoxic cultured neurons, vitamin E inhibited lipid peroxidation and reduced cell death.⁸ It also decreased the degeneration of hippocampal cells after cerebral ischemia⁹ and improved the recovery of motor function after spinal cord injury¹⁰ in animal studies.

Various studies have found significant and positive effects among subjects who received vitamin E.¹¹⁻¹⁵ In a double-blind, placebo-controlled, randomized, multicenter trial comprising patients with Alzheimer disease (AD) of moderate severity, Sano et al.¹⁵ found that 85 patients, after receiving vitamin E (2000 international units [IU] per day) for 2 years, demonstrated significantly slower progression of the disease. Specifically, compared with their counterparts who received placebo, patients who received vitamin E took longer to reach one of the following end points: death, institutionalization, or loss of the ability to perform basic daily activities such as eating, grooming, and using the toilet. Sano et al. did not find significant adverse side effects including cardiac, gastrointestinal, dermatologic, psychiatric, or neurologic symptoms in these patients after taking a megadose of vitamin E for 2 years.

The positive effects of vitamin E also have been reported for patients with vascular dementia and for elderly people without dementia. In a longitudinal, community-based epidemiologic study of 3385 younger men, the combined use of vitamin E and C supplements had a significant protective effect against the occurrence of vascular dementia in their later years. In addition, among men without dementia, the use of either a vitamin E or C supplement was associated with a better cognitive test performance.¹² In two other population-based longitudinal studies, vitamin E intake from foods or supplements was found to be associated with less cognitive decline¹³ and a reduced risk of AD.^{11,14}

In view of the beneficial effects of vitamin E that have been observed in animals, elderly people without dementia, and patients with dementia, the current study evaluated the effect of a megadose of vitamin E

on patients with NPC who develop TLN. Our objective was to determine whether vitamin E could improve the cognitive functioning of these patients. Clinical investigation of possible interventions for patients with cerebral radionecrosis remains very rare. Therefore, the current study was an initial investigation to explore the effects of vitamin E on patients with NPC who have TLN.

MATERIALS AND METHODS

Patient Population

Patients with cerebral radionecrosis after radiotherapy were eligible for the study. The following entry criteria were established: 1) freedom from recurrence for > 5 years; 2) radiologic evidence of TLN; and 3) no mental impairments. Patients with significant psychiatric problems, severe hearing and/or vision loss, or speech problems that might affect their cognitive performance were excluded from the study. The protocol was approved by the institutional review board at the Queen Elizabeth Hospital, and informed consent was obtained from all participants.

The study included 29 patients with NPC who had either unilateral or bilateral TLN. They were recruited from the neurology clinic at the Queen Elizabeth Hospital in Hong Kong and enrolled in the study protocol on a voluntary basis. Of these patients, 19 (15 males and 4 females) were treated with vitamin E and 10 (5 males and 5 females) served as control patients. In the treatment group, 73.7% and 26.3% of patients had bilateral and unilateral TLN, respectively, compared with 70% and 30% of patients in the control group. The presence of unilateral and bilateral TLN was balanced between the two groups ($\chi^2 = 0.05$; degree of freedom [*df*] = 1; not significant). Patients also were matched for age, education, radiation dosage during radiotherapy, time since radiotherapy, and lesion volume (Table 1).

Treatment Plan

A vitamin E dosage similar to the one used in the double-blind, placebo-controlled, randomized, multicenter trial conducted by Sano et al.,¹⁵ was chosen for the current study. Patients in the treatment group received 2000 IU per day of vitamin E for 1 year, delivered at a dose of 1000 IU twice per day.

To ensure the safety of the treatment and patients' full participation, patients' medical conditions, checked via routine blood and urine analyses and drug compliance, were monitored constantly by medical officers during regular medical follow-ups at the clinic. All patients in the treatment group were reported to have complied well with the medication and no significant adverse side effects were observed.

TABLE 1
Demographic and Clinical Characteristics of Patients in the Treatment and Control Groups

Variable	Treatment (n = 19)	Control (n = 10)	t value	P value
	Mean (SD)	Mean (SD)		
Age at treatment (yrs)	57.95 (9.32)	57.10 (13.91)	0.20	0.85
Education (yrs)	8.32 (3.89)	8.80 (6.27)	-0.26	0.80
Radiation treatment				
Total dosage received (Gy)	56.78 (4.72)	59.78 (4.04)	-1.72	0.10
Radiotherapy dosage per fraction (Gy)	3.06 (0.83)	2.56 (0.65)	1.71	0.10
Time since (yrs)	15.47 (5.33)	13.80 (7.45)	0.70	0.49
Total lesion volume (cm ³) ^a	23.03 (24.34)	25.38 (34.02)	-1.76	0.86

SD: standard deviation; Gy: grays.

^aData included 14 patients from the treatment group and 6 patients from the control group.

Neuropsychological Assessment

Neuropsychological tests were administered to each patient by trained examiners before and 1 year after medication. The examiners were blind to the medication received by the patients. Written informed consent was obtained from all patients for assessment before and after treatment.

A Cantonese version of the Mini-Mental Status Examination (CMMSE)¹⁶ was used to determine global cognitive performance. A computerized reaction time attention test developed by one of the authors (A.S.C.) was used to measure patients' sustained attention. Patients were asked to use their dominant index finger to touch a black circle that was flashed in random positions on the computer screen as quickly as possible for 160 trials. The average reaction times in completing the successful trials in terms of milliseconds were recorded in the computer. This type of paradigm was found to be sensitive in detecting attention deficits.^{17,18} The Hong Kong List Learning Test (HKLLT)¹⁹ was employed to measure verbal memory. The Visual Reproduction subtest of the Wechsler Memory Scale-III (WMS-III VR)²⁰ was used to assess visual memory.

Expressive language ability was assessed by the Category Fluency Test (CFT).²¹ A computerized Cognitive Flexibility Test developed by one of the authors (A.S.C.) was used to assess subjects' ability to think flexibly. On a touch-screen monitor, two rows of geometric figures were displayed. Within each row, two circles and two squares were interleaved with each other. The figures in the bottom row were response keys for the patients to touch. In the top row, either one or two figures were randomly flashed simultaneously. The possible combinations were one circle, one square, two circles, and two squares. If one circle was flashed, the subject had to touch two squares. If

one square was flashed, two circles had to be touched. If two circles were flashed, one square had to be touched, whereas one circle had to be touched for two flashed squares. The test included 40 trials and the average reaction times in completing the successful trials in terms of milliseconds were recorded in the computer.

Self-Evaluation on Cognitive Function

In addition to neuropsychological assessment, a questionnaire was administered to the patients with NPC to rate their opinion on 8 cognitive domains, including attention, reading, writing, memory, visual motor ability, expressive ability, computational skills and planning, on a 5-point scale (1 = the worst, 3 = average; and 5 = the best) before and after 1 year. The total score ranged from 8 to 40 points. Higher scores indicated better perceived performance.

Statistical Analysis

We used repeated-measures analysis of variance to evaluate the effect of a megadose of vitamin E on the treatment and control groups before and after medication. The raw scores of the neuropsychological tests for each cognitive function obtained in the two conditions, i.e., before and after medication, were analyzed as within-subject variables, whereas the two groups (i.e., the treatment and the control groups) were regarded as between-subject variables. If the interaction effect was significant, suggesting that the two groups demonstrated a different change in performance before and after 1 year, simple group and condition effects were evaluated further using independent and paired *t* tests, respectively, to determine the pattern of change for each group.

RESULTS

Pretreatment Baseline Performance

Table 2 shows the baseline performance on the neuropsychological tests for the treatment and control groups. There was no significant difference in their performance with respect to global cognitive functioning, attention, memory, language, and executive functioning before treatment.

Effect of Vitamin E on Global Cognitive Functioning

Figure 1 shows the global cognitive functioning of the patients in the treatment and control groups measured by the CMMSE before and after a 1-year treatment period. There was a significant improvement in global cognitive function for patients after 1 year of treatment, with $F(1,27) = 4.90$ and $P = 0.035$. Specifically, the CMMSE score of the treatment group improved significantly, by 5.35% (before treatment: mean [M], 27.32; standard deviation [SD], 2.38; after treatment: M, 28.63; SD, 1.38),

TABLE 2
Baseline Performance on the Neuropsychological Tests for the Treatment and Control Groups

Test	Treatment	Control	<i>t</i> value	<i>P</i> value
	Mean(SD)	Mean(SD)		
Global cognitive functioning				
CMMSE ^a	27.32 (2.38)	26.20 (5.09)	0.81	0.43
Attention				
Average reaction time (ms)	862.16 (291.10)	937.47 (427.42)	-0.56	0.58
Verbal memory				
HKLLT ^a				
Trial 1	4.84 (1.64)	4.80 (2.30)	0.06	0.96
Trial 2	7.42 (2.48)	7.50 (3.34)	-0.07	0.94
Trial 3	8.63 (2.77)	8.50 (3.34)	0.11	0.91
Trial 4	6.58 (2.36)	6.60 (3.92)	-0.02	0.99
Trial 5	5.95 (3.31)	6.30 (3.92)	-0.26	0.80
Visual memory				
WMS-III VR ^a				
Immediate	58.74 (17.60)	65.20 (20.06)	-0.90	0.38
30 min delay	40.32 (24.55)	39.60 (31.09)	0.07	0.95
Language				
Category Fluency ^a	23.32 (4.31)	21.00 (6.78)	1.13	0.27
Cognitive Flexibility				
Average reaction time (ms)	1932.98 (684.42)	1596.51 (430.72)	1.41	0.17

SD: standard deviation; CMMSE: Cantonese version of the Mini Mental State Examination; HKLLT: Hong Kong List Learning Test; WMS-III VR: Visual Reproduction subtest of the Wechsler Memory Scale-III.

^a Raw score.

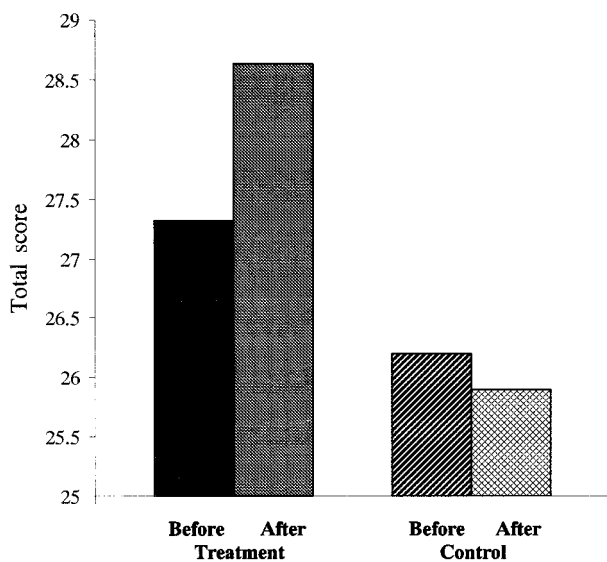


FIGURE 1. Global cognitive functioning of patients in the treatment and control groups as determined by the Cantonese version of the Mini Mental State Examination before and after 1 year of vitamin E treatment. The maximum possible score was 30.

with $t(18) = -3.04$ and $P = 0.007$, after patients received vitamin E for 1 year. No significant change in the CMMSE score was observed in the control group (before treatment: M, 26.20; SD, 5.09; after treatment: M, 25.90; SD, 5.84), with $t(9) = 0.52$ and $P > 0.05$.

Effect of Vitamin E on Verbal and Visual Memory

Figure 2 summarizes verbal learning and memory performance on the HKLLT for both groups before and after treatment. The two groups did not differ in their performance across 5 trials during baseline measurement, with $F(1,27) = 0.003$ and $P > 0.05$. However, after 1 year, the two groups exhibited different patterns of change in their performance on the verbal memory test, with $F(1,27) = 4.86$ and $P = 0.036$. The treatment group demonstrated an average improvement of approximately 27.24% across 5 trials ($P < 0.05$) on the HKLLT, whereas no significant difference was found for the control group ($P > 0.05$).

A similar pattern of change in performance was found for visual memory (Fig. 3). The performance of the two groups was not different on the Immediate Recall Trial, with $t(27) = -0.90$ and $P > 0.05$, or the 30-Minute Delayed Recall Trial, with $t(27) = 0.07$ and $P > 0.05$, of the WMS-III VR before treatment. After 1 year of treatment, a significant improvement was found in visual memory for the treatment group, with $F(1,27) = 8.65$ and $P = 0.007$. Performance improved by 24.56% on the Immediate Recall Trial, with $t(18) = -4.14$ and $P = 0.001$, and by 51.09% on the 30-Minute Delayed Recall Trial, with $t(18) = -4.72$ and $P = 0.000$. No significant change in performance was found for the control group after 1 year ($P > 0.05$).

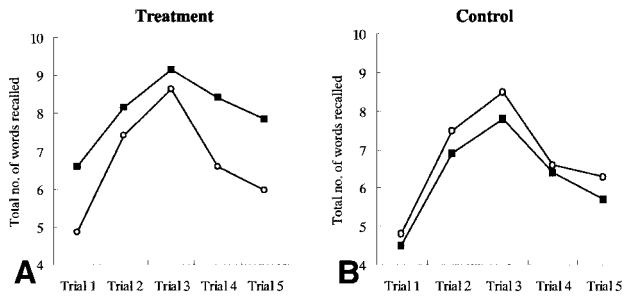


FIGURE 2. Verbal memory performance on the Hong Kong List Learning Test before and after 1 year of vitamin E treatment for patients in the (A) treatment and (B) control groups. Open circles: before treatment; filled squares: after treatment.

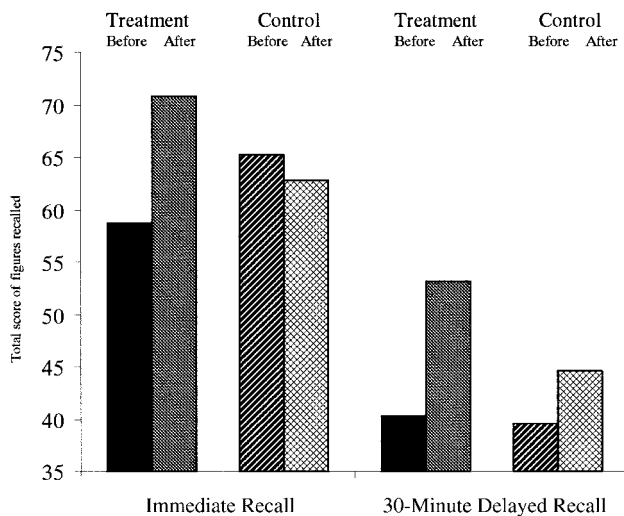


FIGURE 3. Visual memory performance of patients in the treatment and control groups on the Visual Reproduction subtest of the Wechsler Memory Scale-III before and after 1 year of vitamin E treatment.

Effect of Vitamin E on Attention, Language, and Executive Function

There was no significant difference in patients' attention as determined by the average reaction time of the computerized attention test and language ability as assessed by the CFT between the treatment and control groups after treatment. However, in terms of executive function as measured by the computerized Cognitive Flexibility Test, the two patient groups exhibited different changes in performance with respect to average reaction time before and after 1 year, with $F(1,23) = 4.91$ and $P = 0.04$ (Table 3). Further analyses showed that both groups did not differ in their average reaction time on the Cognitive Flexibility Test before medication, with $t(27) = 1.41$ and $P > 0.05$. However, there was a significant improvement in the average reaction time for the treatment group after medication, with $t(17) = 2.31$ and $P = 0.001$, whereas no

significant change in performance was found for the control group ($P > 0.05$).

Self-Evaluation of Cognitive Function

Patients in the treatment group had a minor increase in their subjective ratings after the 1-year treatment with vitamin E (before treatment: M, 24.78; SD, 3.80; after treatment: M, 26.56; SD, 5.81). They perceived improved performance in terms of cognitive function after 1 year of treatment. However, subjective ratings for the patients in the control group slightly decreased (before treatment: M, 25.71; SD, 7.63; after treatment: M, 22.70; SD, 8.51). Statistically, the change in both groups did not reach significance. The possibility that the relatively small sample sizes of the two groups contributed to the nonsignificant result could not be ruled out.

DISCUSSION

To our knowledge, the current study is the first to investigate the effects of vitamin E on the cognitive function of patients with NPC who have TLN. The findings suggest that vitamin E may be a promising complementary intervention for patients with NPC. After 1 year of vitamin E treatment, their global cognitive function as measured by the CMMSE increased by approximately 5%, compared with the nonsignificant change in the control group. In addition, improvements were also found in their memory and cognitive flexibility but not in other cognitive functions, including attention and language. Given that the patients in the treatment group in general perceived better cognitive function after treatment, as indicated in their self-evaluation, the extent of improvement in their performance of neuropsychological assessment may have a significant impact on their daily function.

In contrast, the comparatively limited change in the scores on the neuropsychological assessment of global cognitive function and memory performance may be related to the relatively short duration of the treatment. For instance, in the study conducted by Sano et al. on patients with AD of moderate severity, significantly slower progression of disease was observed after 2 years of vitamin E treatment. Therefore, it is conceivable that the patients in the treatment group may continue to show improvement in their cognitive function with longer duration of vitamin E intake.

Memory impairment is one of the most significant cognitive deficits found in patients with TLN.¹ Many studies have been conducted to evaluate the effectiveness of training on compensatory memory strategies for patients with memory problems. Although specific interventions are aimed at facilitating the acquisition

TABLE 3
Performance on Attention, Language, and Cognitive Flexibility Tests for Patients in the Treatment and Control Groups before and after 1 Year

Test	Treatment		Control		Repeated-measures ANOVA	
	Before	After	Before	After	F	P value
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)		
Attention						
Average reaction time (ms)	862.16 (291.10)	752.31 (232.22)	937.47 (427.42)	828.51 (212.98)	0.00	0.99
Category Fluency ^a	23.32 (4.31)	22.00 (5.73)	21.00 (6.78)	22.10 (5.02)	2.21	0.15
Cognitive Flexibility						
Average reaction time (ms)	1932.98 (684.42)	1664.13 ^b (566.42)	1596.51 (430.72)	1595.86 (382.34)	4.91	0.04

SD: standard deviation; ANOVA: analysis of variance.

^a Raw score.

^b Significant decrease in reaction time.

of specific skills rather than improving memory functioning per se, effective interventions to improve memory performance are lacking.²² Because of the lack of an effective intervention for improving memory, the improvement demonstrated in patients in the current study after 1 year of vitamin E treatment may be clinically significant, not only for the patients with NPC, but also for other brain-damaged patients with memory impairment due to other etiologies. Indeed, our findings are also consistent with results obtained in other studies of elderly patients with or without dementia.¹¹⁻¹⁵ In those studies, the progression of cognitive decline was reported to be slowed by the receipt of vitamin E supplements. Therefore, further investigation of the effects of vitamin E on the cognitive function of other brain-damaged patients with memory complaints may be considered. However, before the delivery of vitamin E can become a clinical treatment to improve memory performance, several issues have to be addressed and resolved to verify the effectiveness of vitamin E.

One limitation of the current study was that the patients were not randomized to the treatment and control groups and they were not blind to the treatment delivered, i.e., the study was not a double-blind, placebo-controlled, randomized study. One may query the reliability of the positive changes found in the treatment group. It is well recognized that a double-blind, placebo-controlled, randomized study is the most ideal research design to evaluate treatment effects. However, before such an ideal study can be performed, preliminary data from clinical studies with well designed controls that allow a comparison between treatment conditions or case studies are also essential for researchers and can be viewed as a stepping stone for further investigation. The findings from the current study can be regarded as such preliminary

data for the future evaluation of the effectiveness of vitamin E on patients with cognitive deficits, particularly with memory impairments. In fact, the recruitment procedure performed at the neurology clinic of the Queen Elizabeth Hospital reduced selection bias to a minimum through open recruitment and the participation of volunteers who provided written consent. Together with the finding that the positive improvements were only observed for certain cognitive functions among patients in the treatment group, the therapeutic effects of vitamin E on cognitive function should not be overlooked and deserve further investigation.

The long-term effect of the treatment also needs to be explored and confirmed in the future. In the current study, the effect of a 1-year treatment period was investigated. However, it is unknown whether the improvements in cognitive function can be increased further after a longer duration of treatment. The Institute of Medicine has determined that the maximum intake of vitamin E is 1500 IU per day because it can act as an anticoagulant and increases the risk of bleeding problems.²³ However, the long-term safety of a high dose of vitamin E intake has not been tested. Before we can evaluate the long-term effect of vitamin E intake, the safety of a high dose on the physical health of the patients should be taken into consideration. Vitamin E supplementation has been shown to reduce cognitive decline in the elderly and to lower the risk of AD.^{11,14} Therefore, the possibility of using vitamin E supplement for long-term treatment may be worth investigating. In addition, it is important to determine whether the effect can be sustained after discontinuation of the treatment. Finally, although the antioxidant function of vitamin E, which is proven to be effective in lipid peroxidation^{24,25} and which prevents the propagation of free radical reaction,^{26,27} is

often emphasized in the studies mentioned for its positive effects, the precise mechanism by which vitamin E improves cognitive function, particularly memory, is not yet known. More studies on this issue are highly recommended before conclusive evidence about the effectiveness of vitamin E as a possible intervention for the cognitive deficits of patients with cerebral radionecrosis can be established.

REFERENCES

- Cheung M, Chan AS, Law SC, Chan JH, Tse VK. Cognitive function of patients with nasopharyngeal carcinoma with and without temporal lobe radionecrosis. *Arch Neurol.* 2000; 57:1347–1352.
- Cheung M, Chan AS, Law SC, Chan JH, Tse VK. Impact of radionecrosis on cognitive dysfunction in patients after radiotherapy for nasopharyngeal carcinoma. *Cancer.* 2003;97: 2019–2026.
- Brown ES, Rush AJ, McEwen BS. Hippocampal remodeling and damage by corticosteroid: implications for mood disorder. *Neuropsychopharmacology.* 1999;21:474–484.
- Wolf OT, Convit A, McHugh PF, et al. Cortisol differentially affect memory in young and elderly men. *Behav Neurosci.* 2001;115:1002–1011.
- Lee AW. Complication of radiation therapy. In: van Hasselt CA, Gibb AG, editors. *Nasopharyngeal carcinoma* (2nd edition). Hong Kong: The Chinese University Press, 1999:255–275.
- Chan PH, Schmidley JW, Fishman RA, Longar SM. Brain injury, edema and vascular permeability changes induced by oxygen-derived free radicals. *Neurology.* 1984;34:315–320.
- Halliwell B, Gutteridge MC. Oxygen radicals and the nervous system. *Trends Neurosci.* 1985;8:22–26.
- Yoshida S, Busto R, Watson BD, Santiso M, Ginsberg MD. Postischemic cerebral lipid peroxidation in vitro: modification by dietary vitamin E. *J Neurochem.* 1985;44:593–601.
- Hara H, Kato H, Kogure K. Protective effect of alpha-tocopherol on ischemic neuronal damage in the gerbil hippocampus. *Brain Res.* 1990;510:335–338.
- Anderson DK, Waters TR, Means ED. Pretreatment with alpha tocopherol enhances neurologic recovery after experimental spinal cord compression injury. *J Neurotrauma.* 1988;5:61–67.
- Marianne EJ, Geerlings MI, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA.* 2002;287:3223–3229.
- Masaki KH, Losonczy KG, Izmirlian G, et al. Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. *Neurology.* 2000;54:1265–1272.
- Morris MC, Evans DA, Bienias JL, Tangney CC, Wilson RS. Vitamin E and cognitive decline in older people. *Arch Neurol.* 2002;59:1125–1132.
- Morris MC, Evans DA, Bienias JL, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA.* 2002;287:3230–3237.
- Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med.* 1997;336:1216–1222.
- Chiu HF, Lee HC, Chung WS, et al. Reliability and validity of the Cantonese version of Mini-Mental State Examination—a preliminary study. *J Hong Kong Coll Psychiatrists.* 1994; 4(Suppl 2):25–28.
- Green RC, Clarke VC, Thompson NJ, Woodard JL, Letz R. Early detection of Alzheimer's disease: methods, markers, and misgivings. *Alzheimer Dis Assoc Disord.* 1997;11(Suppl 5):S1–S5.
- Watanabe A, Kuwabara Y, Okita H, Kato A. Computer-assisted quantitative neuropsychological tests for early detection of subclinical hepatic encephalopathy in patients with liver cirrhosis. *Res Commun Biol Psychol Psychiatry.* 1997; 22:25–38.
- Chan AS, Kwok IC. *Hong Kong List Learning Test.* Hong Kong: The Chinese University of Hong Kong, 1999.
- Wechsler D. *Wechsler Memory Scale—Third Edition: administration and scoring manual.* San Antonio: The Psychological Corporation, 1997.
- Chan AS, Poon MW. Performance of 7- to 95-year-old individuals in a Chinese version of the category fluency test. *J Int Neuropsychol Soc.* 1999;5:525–533.
- Cicerone KD, Dahlberg C, Kalmar K, et al. Evidence-based cognitive rehabilitation: recommendations for clinical practice. *Arch Phys Med Rehabil.* 2000;81:1596–1615.
- Institute of Medicine, Food and Nutrition Board. *Dietary reference intakes: vitamin C, vitamin E, selenium, and carotenoids.* Washington, DC: National Academy Press, 2000.
- Tappel AL. Vitamin E as the biological lipid antioxidant. *Vitam Horm.* 1962;2:493–510.
- Esterbauer H, Dieber-Rotheneder M, Striegl G, Waeg G. Role of vitamin E in preventing the oxidation of low-density lipoprotein. *Am J Clin Nutr.* 1991;53:314S–321S.
- Burton GW, Joyce A, Ingold KU. Is vitamin E the only lipid-soluble, chain-breaking antioxidant in human blood plasma and erythrocyte membranes? *Arch Biochem Biophys.* 1983; 221:281–290.
- Packer L. Vitamin E is nature's master antioxidant. *Sci Am Sci Med.* 1994;1:54–63.