Effect of Acori Graminei Rhizoma (AGR) in combination with Acetyl-L-Carnitine (ALC) in old ages with decreased memory and cognitive functions

Soo Min Sohn[1], Kyoung Ho Shin[2], Pyong Sahm Ku[3], Hoon Choi[4], Hong Kyun Lee[4]

[1]Department of Internal Medicine, Ga Eun Hospital, [2]Department of Rehabilitation Medicine, Daegu Geriatric Hospital, [3]Korea AAM Institute, [4]Department of OB/GYN, Inje University. Korea

Abstract

Objective: There are many known traditional Korean herbs to be effective in improving cognitive functions. *Acori graminei rhizoma* (AGR) is the dry rhizome of *Acorus gramineus soland* and it is known to be helpful in senile amnesia and cognitive function. The aim of this study was to check the additive effect of AGR in subjects taking acetyl-L-carnitine (ALC).

Methods: Forty subjects with decreased memory and cognitive functions evaluated by Global Deterioration Scale (GDS), Clinical Dementia Rating Scale (CDR), Hamilton Rating Scale for Depression (HRDS), Korean version of Mini-Mental State Examination (K-MMSE) and the Modified Barthel Index (MBI) at the time of admission were selected. These tests were applied twice, at baseline and 3 months later.

Results: All 40 subjects (20 subjects for ALC only and 20 subjects for ALC plus AGR tea - 2g of Acori graminei rhizoma in hot boiled water) finished the study without any dropout. There were no significances between the two groups, and between the baseline and after 3 months in both groups with respect to GDS, CDR, HRDS, K-MMSE and MBI. No adverse reactions or laboratory test abnormalities were observed in either group.

Conclusions: No evidence was obtained by objective assessments of any benefit derived from addition of AGR tea in subjects taking ALC. But, further studies should be accomplished.

Key words : Acori graminei rhizoma, global deterioration scale, clinical dementia rating scale, hamilton rating scale for depression, Korean version of mini-mental state examination, modified barthel index

Introduction

Since the population of old age group is growing bigger, various diseases associated with old ages are in concern. Decreasing in memory function and weakening of cognitive function are quite common features in old ages. There are not only drugs but also many other foods including herbs known to be helpful in prevention of memory loss. In Korea, some people take *Acori graminei rhizoma* (AGR) as a tea and it has been known to help in memory and cognitive function declining associated with ages. AGR is the dry rhizome of *Acorus gramineus soland* and it has been used in Korean traditional prescriptions for hundreds of years.

Some of their known actions are sedative, digestive, analgesic, diuretic, and antifungal actions.[1] It also has been used for more than two thousand years mainly for epilepsy and to relive pain in China. But there are few paper describes the experiments on the effects of AGR on memory processes.[2] AGR can be taken in various ways and can be mixed with other herbs. We used small amount of AGR as a tea. Acetyl-L-carnitine (ALC) is one of the drugs known as nootropics and is known to have beneficial effects in improving memory and increasing attention. ALC is usually given orally in tablet or capsule form with dosage ranging from 1-3 grams daily, in divided doses.[3-5] The aim of this study was to find an additive improvement of AGR in memory and cognitive function who are taking ALC for the decrease in memory and cognitive function.

Materials and Methods

Study subjects

Forty subjects (21 females and 19 males) who were admitted to our hospital for more than three months were enrolled in this study. Their average age was 75.21 and they had various underlying medical diseases, such as diabetes mellitus, hypertension, etc.(Table 1) The subjects were divided randomly into two groups, as group 1 was administered ALC and group 2, ALC with AGR tea.

Methods

In this study, testing was performed twice; once before medication (at baseline) and after 3 months of medication. The tests were consist of K-MMSE (Korean version of Mini-Mental State Exam), the GDS (Global Deterioration Scale), the CDR scale (Clinical Dementia Rating), the HRDS (Hamilton Rating Scale for Depression), and the Modified Barthel Index. In addition, all subjects took imaging studies of brain such as CT or MRI to check cerebral infarction. We also determined CBC, BUN/Cr, and AST/ALT before and after 3 months of medication.

The tests

1) Global Deterioration Scale (GDS)
This test provides an overview of the stages of cognitive function for those suffering from a primary degenerative dementia and it is broken down into 7 different stages.[6-7]
2) Clinical Dementia Rating Scale (CDR)
CDR is commonly used to evaluate cognitive and functional performance in old ages with Alzheimer's dementia or other types of dementia. It is composed of 6 parts including memory, orientation, decision making, problem solving, social activities, housework, habits and hygiene. Each part can be scored as 0, 0.5, 1, 2, 3.[8]

3) Hamilton Rating Scale for Depression (HRDS)
It is a 17-item scale that evaluates depressed mood, vegetative and cognitive symptoms of depression, and comorbid anxiety symptoms. The 17-items are rated on either a 5-point (0-4) or a 3-point (0-2) scale. In general, the 5-point scale items use a rating of 0 : absent, 1 : doubtful to mild, 2 : mild to moderate, 3 : moderate to severe, 4 : very severe. The 3-point scale items used a rating of 0 : absent, 1 : probable or mild, 2 : definite.[9]
4) Korean version of Mini-Mental State Examination (K-MMSE)
This test was translated and standardized from MMSE (Mini-Mental State Examination) developed by Folstein et al and checks orientations (time and place), memory registration, concentration, calculation skill, recall memory, and speech. The maximum possible total test score is 30 points.[10-12]
5) Modified Barthel Index (MBI)
Barthel consists 10 items which look at personal ADL, ambulation, toileting and transfer etc. A score of 100 mean independence and clinically less than 40 is thought to carry a high risk of needing institutional care.[13-14]

Medication

All subjects took 1500mg of acetyl-L-carnitine daily and among those, 20 subjects drank AGR tea twice a day. We used 2g of *Acori graminei rhizoma* in hot boiled water for tea. Subject compliance was checked daily, and all subject continued to take without any change.

Statistical analysis

K-MMSE, GDS, CDR, HRDS, and MBI data were collected twice before and after 3 months of medication. Wilcoxon signed rank test and Wilcoxon rank sum test were used for the statistical analysis.

Table 1. General characteristics of the study subjects

		ALC only	ALC +AGR
	Sex	11 female + 9 male	10 female + 10 male
	Mean age	73.58±8.29	76.49±5.34
	Mean duration of education	7.52±4.76	7.21±3.58
Underlying diseases	hypertension (present : none)	15 : 5	13 : 7
	DM (present : none)	9 : 11	12 : 8
	hyperlipidemia (present : none)	4 : 16	3 : 17
	liver disease (present : none)	2 : 18	3 : 17
	cardiac disease (present : none)	6 : 14	2 : 18
	pulmonary disease (present : none)	3 : 17	1 : 19

Table 2. Measurement scale of ALC only and ALC + AGR group

		ALC only (mean±SD)	ALC +AGR (mean±SD)	p-value
GDS	baseline	3.42±1.42	3.13±0.27	
	after 3 months	3.61±1.31	3.24±0.53	0.4258
	p-value	0.6912	0.8124	
CDR	baseline	1.81±0.84	1.53±0.49	
	after 3 months	2.02±0.92	1.61±0.83	0.8356
	p-value	0.7545	0.7358	
HRDS	baseline	12.58±7.57	13.57±5.62	
	after 3 months	12.25±4.85	12.98±7.35	0.6984
	p-value	0.8562	0.4291	
K-MMSE	baseline	11.89±8.58	13.02±5.64	
	after 3 months	11.53±9.12	12.87±7.36	0.9352
	p-value	0.6481	0.7633	
MBI	baseline	42.37±18.59	47.82±16.43	
	after 3 months	44.32±16.83	46.75±18.99	0.8352
	p-value	0.9357	0.5648	

Results

All 40 subjects took 1500mg of ALC daily for 3 months without any change and 20 subjects drank AGR tea two times a day. No side effects were observed. Table 1 shows the general characteristics of the study subjects. We used chi-square test for statistical analysis but the number of the group was small and there were no significant differences in sex, age, duration of education, or their underlying associated diseases, such as hypertension, diabetes mellitus, cardiac diseases, liver diseases, hyperlipidemia, and pulmonary diseases between the ALC only group and the ALC +AGR group.

1. Global Deterioration Scale (GDS)

The stage of GDS at baseline in ALC only group was 3.42 $\pm$1.42 and in the ALC +AGR group 3.13 $\pm$0.27. GDS stage after 3 months in ALC only group was 3.61 $\pm$1.31 and in the ALC +AGR group 3.24 $\pm$0.53 (p = 0.4258). There was no significant difference between these two groups and also between the baseline and after 3 months in both groups.

2. Clinical Dementia Rating Scale (CDR)

The clinical dementia rating scale is composed of 6 parts and the mean score of all 6 parts at baseline in the ALC only group was 1.81 $\pm$0.84 and in the ALC +AGR group 1.53 $\pm$0.49, and the score after 3 months in the ALC only group was 2.02 $\pm$0.92 and in the ALC +AGR group 1.61 $\pm$ 0.83 (p = 0.8356). There was no significant difference between these two groups and also between the baseline and after 3 months in both groups.

3. Hamilton Rating Scale for Depression (HRDS)

The points at baseline in the ALC only group was 12.58 $\pm$ 7.57 and in the ALC +AGR group 13.57 $\pm$5.62, and the points after 3 months in the ALC only group was 12.25 $\pm$ 4.85 and in the ALC +AGR group 12.98 $\pm$7.35 (p = 0.6984). There was no significant difference between these two groups and also between the baseline and after 3 months in both groups.

4. Korean version of Mini-Mental State Examination (K-MMSE)

The K-MMSE score at baseline in the ALC only group was 11.89 $\pm$8.58 and in the ALC +AGR group 13.02 $\pm$5.64, and the score after 3 months in the ALC only group was 11.53 $\pm$9.12 and in the ALC +AGR group 12.87 $\pm$7.36 (p = 0.9352). There was no significant difference between these two groups and also between the baseline and after 3 months in both groups.

5. Modified Barthel Index (MBI)

The total Modified Barthel Index score at baseline in the ALC only group was 42.37 $\pm$18.59 and in the ALC +AGR group 47.82 $\pm$16.43, and the total score after 3 months in the ALC only group was 44.32 $\pm$16.83 and in the ALC +AGR group 46.75 $\pm$18.99(p = 0.8352). There was no significant difference between these two groups and also between the baseline and after 3 months in both groups.

6. Other Tests

CBC, BUN/Cr, and AST/ALT showed no change between the baseline and after 3 months in either group.

Discussion

There are many herbs known to be helpful in cognitive functions, but their ingredients and active functions are not known exactly. Some people take these herbs in a hot boiled water as a tea or as an extract or in various ways. Also there are some traditional Korean drugs such as Chongmyungtang, the combination of *Acorus gramineus*, *Polygala tenuifolia* and *Poria cocos*. It has long been employed in the clinical treatment of mental disorder such as senile amnesia in Korea, although a very few studies on its pharmacological effect on the central nervous system has been performed.[15] *Acori graminei rhizoma* (AGR), the rhizome of *Acorus gramineus soland*, whose property, flavour and channel tropism is pungent in flavour, warm in property, acting on the heart and stomach channels, has the effects of inducing resuscitation, tranquilizing the mind, resolving dampness, and regulating the functions of the stomach. This herb is one of the popular drugs in traditional Korean medicine, which has been used to treat loss of consciousness and confusion of the mind due to mental disturbance by pathogenic dampness in the course of febrile diseases, and palpitation, insomnia, amnesia and tinnitus due to insufficiency of the herat-qi.[16]

The aim of this study was to check the additive positive effect of AGR in improving decreased memory and cognitive functions. According to the results of GDS, CDR, HRDS, K-MMSE and MBI, there was no significant difference between these two groups and also between the baseline and after 3 months in both groups.

The number of the study group was small and the duration was also short to check for the difference between ALC

only group and ALC +AGR group. Another problem in this study was the amount of the AGR used to make a tea. Usual amount of the AGR in Korean traditional medicine is known to be 3 - 9g but we used smaller than this (1 - 2g). *Acorus gramineus soland* (Araceae) is a rheophyte and is distributed in southeastern Asia.[17-18] According to most authors, *Acorus* includes two species, *A. calamus L.,* from eastern North America and eastern template Asia (Siberia and Manchuria), and *A. gramineus Ait.,* from Japan and Southeast Asia.[19-20] The drug *Acori* is also called sweetflag. It is a frequently used and has been used in China for more than 2000 years. It can be used for the treatment of diseases such as feelings of stiffness and fullness in the chest and upper abdomen, anorexia, appetite-prohibiting dysentery, epidemic febrile diseases with symptoms of high fever, epilepsy, amnesia and deafness. According to some ancient books, *Acori* also has effects like supplementing, calculated to prolong man's life, stopping bleeding, preventing abortion, invigorating blood circulation, removing blood stasis, dispelling wind and demons, clearing away heat, detoxification, poisoning parasites and stopping itch.[21] It also has been used in Korea for many centuries as a therapeutic agent for cerebral diseases. Studies about the effect of AGR extract showed a diverse response of blood pressure and regional cerebral blood flow[22] and pial arterial diameters in animals.[23] There was a study about central inhibitory effects of water extract of AGR in mice.[24] Also there were some other studies such as their anti-inflammatory effect for skin diseases[25] and anti-bacterial effect.[26-27] Like Chongmyungtang in Korea, there are some studies about traditional Chinese medicinal prescription such as DX-9386.[28-31]

AGR has long been used in various symptoms in Korea but there are not many studies about its effect on memory and cognitive functions. Further studies should be accomplished.

References

1. Cho JS, Joo NE et al. Inhibition of excitotoxic neuronal death by methanol extract of Acori graminei rhizoma in cultured rat cortical neurons. *Journal of Ethnopharmacology* 2000;73:31-7.
2. Yueping Z, Hiroshi S, Nobuyoshi N. Effects of Acorus gramineus Soland on learning and memory performances in mice. *Shoyakugaku Zasshi* 1992;46:103-8.
3. Acetyl-l-carnitine. *Altern Med Rev* 1999;4:438-41.
4. Spagnoli A, Lucca U, Menasce G et al. Longterm acetyl-l-carnitine treatment in Alzheimer's disease. *Neurology* 1991;41:1726-32.
5. Kidd PM. A review of nutrients and botanicals in the integrative management of cognitive dysfunction. *Altern Med Rev* 1999;4:144-61.
6. Reisberg B, Ferris SH, de Leon MJ, and Crook, T. Modified from Global Deterioration Scale. *Am J Psychiatry* 1982;139:1136-39.
7. Eisdorfer C, Cohen D, Paveza GJ et al. An empirical evaluation of the Global Deterioration Scale for staging Alzheimer's disease. *Am J Psychiatry* 1992;149:29.
8. Morris JC. The Clinical Dementia Rating (CDR): Current version and scoring rules. *Neurology* 1993;43:2412-14.
9. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol* 1967;6:278-96.6.
10. Kang YW, Na DL, Hahn SH. A Validity Study on the Korean Mini-Mental State Examination (K-MMSE) in Dementia Patients. *J Korean Neurol Assoc* 1997;15:300-7.
11. Folstein et al. "Mini-Mental State" : a practical method for grading the cognitive state of patients for cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:196-8.
12. Ferris SH, Mackell JA, Mohs R et al. A multicenter evaluation of new treatment efficacy instruments for Alzheimer's disease clinical trials. *Alzheimer Dis Assoc Disord* 1997;11:1-12.
13. Surya et al. Modified scoring for the Barthel Index. *J Clin Epidemiol* 1989;42.
14. Hocking C, William M, Broad J, Baskett J. Sensitivity of Sha, Vanclay and Copper's Modified Barthel Index. *Clin Rehab* 1999;13:141-7.
15. Jang KJ, Lee KH, Kim SL, Choi DY et al. Chongmyungtang attenuates kainic acid-induced seizure and mortal effect in the mouse. *Arch. Pharm. Res* 1997;20:375-8.
16. Kim YO, Kim YS, Leem KH et al. Neuroprotective effects of Acori Graminei Rhizoma on the brain ischemia induced by four-vessel occlusion in rats. *Kor J Herbalogy* 2000;15:79-85.
17. LC Liao, JY Hsiao. Relationship between population genetic structure and riparian habitat as revealed by RAPD analysis of the rheophyte Acorus gramineus Soland. (Araceae) in Taiwan. *Molecular Ecology* 1998;7:1275-81.
18. Matyas B, Peter K Endress. Floral structure and

development of acoraceae and its systematic relationships with basal angiosperms. *Int J Plant Sci.* 2000;161:23-41.

19. Ohwi J. Flora of Japan. Smithsonian Institution Press, Washington D.C. 1965.

20. Sherwin C, Edward L Schneider. Origins and nature of vessels in *monocotyledons. I. Acorus. Int J Plant Sci* 1997;158:51-6.

21. Wang HZ, Chen YG, Fan CS. Review of studies on chemical constituents and pharmacology of genus *Acorus* in China. *Acta Botanica Yunnanica* 1998;96-100.

22. Jeong HW, Kang SY, Bak SW. Effect of Rhizoma Acori Graminei extract on blood pressure and regional cerebral blood flow in rats. *Kor J Herbalogy* 1999;14:81-8.

23. Lee GS, Jeong HW, Kang SY. Mechanism study of Acori Graminei Rhizoma on the pial arterial diameter in rats. *Kor J Herbalogy* 2000;15:1-7.

24. Jyh FL, Sung YH, Yiing MJ, Li LY, Chieh FC. Central inhibitory effects of water extract of *Acori graminei rhizoma* in mice. *Jethnopharmacol* 1998;61:185-93.

25. Mineo S, Takayasu M, Kaori H, Yoshiko T, Taisuke S et al. Studies on Bathing Agent I. Anti-inflammatory effect of bathing agent used for skin disease. *Shoyakugaku Zasshi* 1993;47:1-4.

26. Kim HK, Moon KH, Ryu SY, Moon DC, Lee CK. Screening and Isolation of antibiotic resistance inhibitors from herb materials IV - resistance inhibitors from *Anetheum graveolens and Acorus gramineus. Arch. Pharm. Res* 1998;21:734-7.

27. Oh DH. Antimicrobial activities of *Thuja orientalis L.* and *Acoru graminens Scoland* on the harmful microorganisms. *J Agr Sci* 2000;11:47-55.

28. Nobuyoshi N, Yueping Z, Ken T, Hiroshi S. Effects of DX-9386, a traditional Chinese Preparation, on Passive and Active Avoidance Performances in mice. *Biol Pharm Bull* 1994;17:1472-6.

29. Nobuyoshi N, Yueping Z, Hiroshi S. Ameliorative effects of chronic treatment using DX-9386, a traditional Chinese prescription, on learning performance and lipid peroxide content in senescence accelerated mouse. *Biol Pharm Bull* 1994;17:1481-4.

30. Nobuyoshi N, Yueping Z, Hiroshi S. Beneficial effects of DX-9386, a traditional Chinese prescription, on memory disorder produced by lesioning the Amygdala in mice. *Biol Pharm Bull* 1994;17:1679-81.

31. Miroslav S, Hiroshi S, Nobuyoshi N. Hoelen (Poria Cocos Wolf) and Ginseng (Panax Ginseng C. A. Meyer), the ingredients of a Chinese prescription DX-9386, Individually promote Hippocampal long-term potentiation in vivo. *Biol Pharm Bull* 1995;18:518-22 .