2004. Vol. 25. No. 4. *129-138*
Korean Journal of Oriental Medicine

Original Articles

A Pilot Study to Assess the Effect of *Gami-Jiwhang-Tang* on Cognitive Effects in Healthy Children

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Objective : Treatments for patients with mental retardation and pervasive developmental disorders are not curative, and are designed to help those with disabilities adjust to their environments and daily demands. As clinicians, the present authors tried to find agents with potentially curative properties. Among the numerous herbal formulations available, we chose and assessed Gami-jiwhang-tang (GJT) in the hope that it would improve cognitive development of children.

Methods : Subjects were typically-developing healthy, 7- to 8-year-old boys and girls living in Seoul, Korea. The experimental group took GJT for six weeks and was followed up six weeks after discontinuation of GJT. The control group was assessed at the same intervals but did not receive placebos. To measure the effects of GJT, neuropsychological tests and intelligence test were taken before commencing GJT and twelve weeks later.

Resulets and Conclusion : For all of the ANOVAs, the treatment by time interaction terms was not significant. However, the experimental group showed the tendency to be progressed in most subscales compared with the control group, especially on performance intelligence, visual organization, and verbal fluency. Conclusion: Although GJT failed to reveal significant improvement in cognition, we remain hopeful about the compound and believe that it should be evaluated by a double-blind, placebo-controlled trial in the future.

Key Words: *Gamijiwhangtang*, intelligence, cognition, children - herbal medicine

Introduction

Mental retardation and pervasive development disorders (PDDs), two developmental disorders, together affect over 1% of the general population (AAMR, 1992; Ritvo et al., 1989). However, despite substantial advances in modern medicine (Aman et al., 2003; McDougle and Posey, 2003) and although early access to rigorous multimodal treatment shows significant improvement in comorbid symptoms in such children, no feasible treatment for core symptoms other than specialized education exists.

Considering that mental retardation and PDDs are life-long disabilities, etiologic and curable managements are desperately needed. Although researchers in

Received 29 Octorber 2004; Received in Revised from 8 November 2004; Accepeted 13 November 2004
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traditional herbal medicine are very active in Asian countries, studies of therapeutic agents for core disabilities of mental retardation and PDDs in children are rare. Several reports suggested improvement in intelligence performance with complex Complementary and Alternative Medicine (CAM) therapies including herbal medication (Zhou et al., 1993; Liu et al., 1994; Tian et al., 1995). These results showed effects with multiple therapies, not with herbal medication only. There were also animal study reports about improved cognitive performance with herbs (Chan et al., 2003; Lin et al., 2003).

In Western medicine, the psychopharmacologic approaches for patients with mental retardation and PDDs are mostly confined to behavioral management. Some results have suggested incidental cognitive improvements with medication like fluoxetine (DeLong et al., 1998; Horsfield et al., 2002). Donepezil given to children with autistic disorder was observed to decrease irritability and hyperactivity, but no changes in inappropriate speech (Hardan and Handen, 2002).

We have focused on agents with potential therapeutic utility in children afflicted with mental retardation or autism ever since the publishing of the report by Eriksson et al. (1998) on neurogenesis in the central nervous system of the human being. In particular, we have paid attention to agents with such potential among the wide range of preparations currently in use in herbal medicine. Herbal medicine has a long history, more than several thousand years. Whereas herbal therapy may seem like an ancient medicine, it is also a kind of progressive modified modern medicine.

Gami-jiwhang-tang (GJT) appears to be a good candidate. On Dong-E-Bo-Gam (Huh, 1975) reported, "The child who can not speak till five years old was regarded as incurable or disabled. After about half a year using GJT and Bojungikitang, the child started to speak one or two words. And after one year passed, the child could speak well." Very similar formulations of GJT are employed as a kind of restorative medicine for children with developmental delays and also for adults with renal diseases or diabetes mellitus (Cho, 1999; Lee et al., 1990; Lee and Park, 1996). In a review by Lee et al. (1990), Liuweidihuang-tang-jia-wei, a very similar preparation to GJT showed facilitation of growth, development of intelligence through brain activation, and improvement of immunity via prolongation of the presence of antibodies. In preclinical experiments with this formulation, GJT caused increased cell proliferation in dentate gyrus of young rats (Kim et al., 2002), protected against alcohol-induced decrease in new cell formation in the rat dentate gyrus (Bahn et al., 2002b) and protected against H_2O_2-induced apoptosis in hippocampal neuronal cells (Shin et al., 2003).

The present study was undertaken to determine whether GJT causes changes in cognitive functions in children.

Materials and Methods

1. Herbal formulatopn

The formulation of GJT was based on Dong-E-Bo-Gam (Huh 1975). The ingredients of this formulation are as follows: Rehmanniae Radix 16g, Dioscorae Radix 8g, Corni Fructus 8g, Alimatis Rhizoma 6g, Moutan Cortex Radicis 6g and Holen 6g (the ingredients for Jiwhangtang, also called as Yukmi or Liuweidihuang) with the addition of Maximowicziae Fructus 8g, and Cervi Cornu 4g, this becomes GJT. All ingredients for our study were obtained from the Gyungdong herbal marketplace, Seoul, Korea, and were washed, dried, and ground, to which honey was added, and the resulting mass was made as whan (a Korean term means a unit of herbal formulation, tablet-like).

Because no rules govern the terminology for herbal formulations, similar terms for one formulation may be

used (Park et al., 2002). In the case of GJT, Liu-Wei-Dihuang (Wang et al., 1998), Liuweidihuangtang (Bahn et al., 2002b), Liuweidihuangtang-jia-wei (Bahn et al., 2002a), Shenqiwan (Kim et al., 2002, Shin et al., 2003), YukMiGiHwangTang (Lee and Park 1996), and Yukmi (Kim et al., 2000) are used for very similar formulations.

The terms 'Gami' (a Korean word) and 'jia-wei' (a Chinese word) mean 'addition.'

2. Subjects

Subjects in this study consisted of healthy children (not diagnosed of any major illness) of either sex in their first and second years of private primary schools in Seoul, Korea. Although GJT has already been proved as a safe and good medicine for health (Cho, 1999), GJT has not been confirmed as a cognitive enhancer yet. Therefore, we decided to select healthy children as subjects instead of the patients with mental retardation or PDDs. Subjects were enrolled in the study after written informed consent was obtained from their parents. Following surveys on developmental history, pre-medication examinations, and psychiatric interviews all children with physical or psychiatric disorders were excluded.

Initially, the experimental group included 27 children (21 boys, 6 girls), and the control group included 26 children (16 boys, 10 girls). In the experimental group, 2 subjects dropped out because of subjects' unwillingness to consume the herbal formulation, not due to complications of the formulation. Thus, the dropout rate was 7.4% for the experimental group. In the control group, 9 members failed to finish the experiment (drop-out rate, 34.6%). In our opinion, this high dropout rate in the control group was related to the design of the study, which was not placebo controlled, and in keeping with Korean culture. Because Korean students, even in the first or second grade of elementary school, are busy with the burdens of extracurricular schedule, their parents did not want to repeat the same tests on their children when no medicine was involved. In all, 25 children (20 boys, 5 girls) in the experimental group and 17 youngsters (10 boys, 7 girls) in the control group completed the study. Parents decided which group (experimental or control) each subject would be assigned to.

3. Methods

Subjects of the experimental group received GJT treatment at a dose of 18 g/day (about 55 whans of GJT/day) for 6 weeks starting from the completion of the preliminary physical and psychiatric examinations. Following six weeks of GJT and a subsequent six-week follow-up period, several examinations, including intelligence test, were carried out. Subjects in the control group underwent the same schedule (Table 1). This was an open-label study, lacking placebo and blinded controls.

4. Examination tools

The parents of the subjects were asked to complete questionnaires, which included demographic information and developmental history from birth to age 6. We developed the questionnaire for this study.

Physical check-ups were repeated 3 times and included height and weight, complete blood count/differential count (CBC/DC), urinalysis (U/A), electrocardiography (ECG), and chest X-ray (posterior-anterior view) (chest PA). These tests were done to ensure good health for all subjects and to protect participants from unknown or unexpected complications of the herbs.

To assess cognition, we examined neuropsycholo gical tests and intelligence test. Three clinical psychology trainees, supervised by a clinical psychologist, carried out neuropsychological evaluation

including the intelligence test. Each subject was tested initially and 12 weeks later by the same examiner. The Hebb-Digit (Milner, 1980), Corsi-Digit (Milner, 1980), Trail Making A and B (Mitrushima et al., 1999), Bender-Gestalt Test, Visual-Motor Integration (VMI)(Beery, 1967, 1982), a verbal fluency assessment (Thurston and Thurston, 1943), and a learning ability test (Hebb, 1961; Corsi, 1972) were used for neuropsychological assessment. The KEDI-WISC (Korean Educational Development Institute-Wechsler Intelligence Scale for Children) (Park et al., 1991) was used to evaluate intelligence. Subtests from these tests (intelligence, visual organization, visuospatial test, memory and learning, attention, language and verbal concept formation, and verbal fluency) were analyzed.

5. Statistical analysis

Student's t-test was carried out to compare the sociodemograhic data, weight, and height. Repeated two-way Analysis of Variance (ANOVA) and paired t-test were carried out for repeated assessment on the same subjects. SPSS version 11.0 was employed for the statistical calculations.

Results

No significant differences existed between the experimental and the control group in terms of the age of the subjects, the ages of their parents, level of mothers' education, socioeconomic status (Table 2). However, level of education of fathers in the control group was significantly higher (t= -2.86, p< .01) than that of fathers in the GJT group.

In height and weight, no significant changes were observed between the groups (Table 3). There were no significant changes in laboratory findings (including CBC/DC, U/A, ECG, chest PA results) between the experimental and control groups.

As assessed by ANOVA (Table 4), no significant differences were found between two groups in terms of cognitive functions. The ranges of interaction terms (Group by Time of measurement) extended from a low of F=.001 (1,39) to a high of F=3.76 (1,38), p>.05. There were significant changes in time factor on some subscores, such as performance intelligence quotient (PIQ) (F=13.29, p<.001), full scale IQ (FSIQ) (F=8.08, p<.01), word fluency test (animal) (F=5.20, p<05), word fluency test ('ㅅ') (F=7.67, p<.05), and Trail making test B(F=13.73, p<.001).

Paired t-tests, performed on test results obtained before and after treatment, revealed that the experimental group showed a significant increase on the PIQ indicated by paired t-tests on scores obtained before and after treatment (t = -3.55, p < .01); the experimental group outperformed the control group in terms of the FSIQ (t = -2.47, p< .05) (Table 5). Both the experimental and control groups made similar gains in terms of attention (Hebb-digit - experimental group: t = -3.81, p < .01, control group: t= -4.39, p< .01; trail making B - experimental group: t= 3.13, p < .01, control group: t = 2.60, p < .05) (Table 5). However, on all items for visual organization, the experimental group revealed significant improvement than the control group. The experimental group also exhibited better performance in verbal fluency (animal) than the control group did (experimental group: t=-3.13, p<.01, control group: t=-1.09).

Discussion

To our knowledge, this is the first study of GJT to assess cognitive function in children. Though Yukmijihwangwan, a very similar formulation to GJT, has been considered effective for improving cognition and language acquisition (Lee et al., 1990), traditional textbooks on herbal formulation do not provide

statistical data.

There were no significant demographic differences between the experimental and control groups except educational attainment of the fathers. The decision of whether to be in the experimental group or the control group was made by subjects' parents, and the ability of the child to consume the herbal formulation may have been one of the deciding factors. We suspect that the sociodemographic characteristics of the families may have influenced such a decision. If parents had higher education and higher SES, this may have caused them to choose less herbal formulation than less educated parents. However, in reports from Canada and the U.S. (Eisenberg et al., 1998; Millar, 1997; Unutzer et al., 2000), CAM users (including users of herbal medicine) were higher income groups and more highly educated than non-users. This difference may be related to cultural differences. Further research is needed on this issue.

There were no significant differences in laboratory findings, weight, or height between groups 12 weeks after commencement of herbal formulation. It is not necessarily appropriate to conclude that GJT has no effect on these variables, as any effect may take a substantial time to show any changes. Greater duration of herbal treatment, different dosages of GJT, and/or more sensitive tests may show sensitivity to treatment.

There were no significant ANOVAs changes for cognition. However, we could find very interesting results from the experimental group. Actually, as seen on Table 2, most sociodemographic factors, weight, height, and even IQ of the control group were slightly higher than those of the experimental group initially, although they were not statistically significant. And also as seen on Table 4, mean values of most subscales in the control group were superior to those of the experimental group before medication. After medication, these superiorities changed. There was a tendency which many variables of the experimental group approximated or went ahead those of the control group. Among them, performance IQ, subscales for visual organization, and word fluency tests were predominant. These subscores were almost consistent with subscores of time factor changes in ANOVAs. This trend does not mean GJT had the effect for the improvement of the cognition. However, it could suggest that GJT might have a potentiality.

Although there were no significant ANOVAs changes for cognition, we also decided to compare within-group changes using paired t-tests. These exploratory analyses seemed justified because there were some marginal interactions on several ANOVAs analyses, although they did not reach statistical significance. With the paired tests, some variables changed significantly in both groups. There were no variables that improved only in control group, whereas there were some variables that improved only in experimental group. In particular, improvement of the subscores associated with visual organization and verbal fluency in the t-test comparisons may be consistent with the description of Dong-E-Bo-Gam (Huh, 1975) regarding GJT effects. This can be also indirect evidence that the herbal formulation might be effective for cognitive improvement. The experimental group exhibited a greater increase in the PIQ than the control group did, but there was no significant change in the VIQ. The experimental group's superiority on the FSIQ was probably due to the increase of PIQ.

There were a number of limitations in the present study. These included the small sizes of the groups, the relatively short period of treatment (compared to clinical studies in Oriental medicine), a lack of gender matching of the subjects, a lack of random assignment, and a the lack of long-term follow-up data. The fact that the subjects of both groups were all healthy individuals with busy school lives (thus not subject to

control on a variety of non-experimental factors) may have posed an additional problem. The significant paired t-test differences reported here should only be viewed as exploratory, as the omnibus ANOVAs were negative.

Conclusion

Although GJT did not show significant improvement in cognition as assessed by ANOVAs, at least a trend of improvement in cognitive function was observed when t-tests were used to compare the changes over time. Therefore, we hope to do further research with this formulation using a double-blind, placebo-controlled design in the future.

Acknowledgement

This work was supported by a grant from Doorhi Oriental Medical Clinic (2000). Authors also wish to thank Professor Michael G Aman, PhD, Nisonger Center for MR/DD, OSU, for his kindness in reviewing this manuscript and for constructive comments.

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Table 1. Schedule for Examinations

	Before Treatment (Base)	6 weeks after commencement (Week 6)	6 weeks after completion (Week 12)
Height & Weight	X	X	X
Questionnaires*	X		
Lab tests**	X	X	X
N-P tests***	X		X

* Questionnaires on developmental history (based on the mother's account)
** Lab tests : CBC/DC, U/A, ECG, Chest PA
*** Neuropsychological tests and intelligence evaluation

Table 2. Sociodemographic Factors(mean±SD)

		Experimental group (n=24)	Control group (n=17)	*t*-value
Age of subjects (months)		84.42±7.62	85.94 ±7.26	-.64
Age of parents (years)				
	Father	38.58±3.50	39.18±4.15	-.49
	Mother	36.96± 3.18	36.94±3.86	.01
Educational level of parents (years)				
	Father	15.25±1.53	16.56±1.20	-2.86**
	Mother	15.25±1.86	15.88±1.82	-1.02
SES# (high:middle:low)		6:17:1	7:10:0	χ^2=1.59

** $p < .01$
#Socio-Economical Status: This classification depended upon parents' income.

Table 3. Weight and Height Changes Following Administration of Preparation [mean (SD)

	Before commencement		*t*-value	6 weeks after commencement		*t*-value	12 weeks after commencement		*t*-value
	Experi-mental group (n=24)	Control group (n=16)		Experi-mental group (n=24)	Control group (n=14)		Experi-mental group (n=22)	Control group (n=15)	
Weight (kg)	24.15 (5.01)	26.31 (3.45)	-1.61	25.15 (5.24)	26.82 (3.96)	-1.11	25.34 (4.46)	27.63 (3.50)	-1.74
Height (cm)	123.60 (5.73)	124.25 (5.13)	-.37	124.35 (5.44)	124.75 (5.15)	-.21	124.47 (4.63)	125.86 (5.10)	-.85

Table 4. Results of Repeated Two ANOVA Before and After Treatment [mean (SD)]

	Before Treatment		After Treatment		F value/df
	Experimental group (n=25)	Control group (n=17)	Experimental group (n=25)	Control group (n=17)	
INTELLIGENCE					
FIQ	117.48 (10.48)	120.18(8.58)	121.36(10.17)	123.47 (8.42)	.05/1, 40
VIQ	116.0(9.85)	117.59 (11.29)	116.56(10.47)	120.82 (8.21)	1.03/1, 40
PIQ	115.12 (12.26)	117.41(6.54)	122.20(12.42)	121.00 (9.35)	1.42/1, 40
VISUAL ORGANIZATION					
Picture completion	11.08 (2.37)	11.00(1.65)	12.52(2.31)	11.35(1.57)	2.09/1, 40
Picture arrangement	10.72(2.22)	11.53(2.03)	11.96(1.98)	11.76(2.90)	1.66/1, 40
Object assembly	12.24(2.42)	12.82(1.62)	13.20(2.21)	13.82(2.18)	.94/1, 40
VISUOSPATIAL TEST					
VMI	15.04(2.40)	16.06(2.86)	15.25(2.48)	16.29(3.07)	.001/1, 39
Block design	14.72 (2.83)	14.35(2.91)	15.28(3.19)	15.18(3.10)	.13/1, 40
MEMORY & LEARNING					
BGT recall	3.52(1.44)	4.13(1.50)	3.81(1.64)	4.81(1.64)	.41/1, 38
Hebb recurring span	3.38(2.41)	2.56(2.55)	3.38(2.35)	4.06(3.10)	3.76/1, 38
Corsi recurring span	2.96(2.11)	2.56(2.06)	3.33(2.12)	3.50(1.96)	.42/1, 38
ATTENTION					
Digit span	11.47(2.29)	12.93(1.87)	11.53 (1.92)	12.43(1.91)	.49/1, 38
Arithmetic	10.92(2.39)	10.65(2.09)	11.24(2.00)	11.41(1.83)	.53/1, 40
Hebb-digit	5.42(0.71)	5.63(0.61)	5.88(0.85)	6.19(0.65)	.33/1, 38
Corsi-digit	5.17(0.76)	5.06(0.57)	5.37(0.82)	5.31(0.60	).02/1, 38
Trail making A	64.62(27.21)	56.81(17.95)	58.58(29.66)	54.50(12.47)	-.60/1, 38
Trail making B	115.04(53.03)	92.13(23.16)	91.33(44.05)	77.44(24.10	)-.75/1, 38
LANGUAGE AND VERBAL CONCEPT FORMATION					
Information	14.00(3.30)	14.71(2.81)	13.40(3.40)	14.29(2.88	)-.06/1, 40
Similarity	13.40(2.19)	14.41(2.52)	13.68(1.79)	14.29(1.61)	.22/1, 40
VERBAL FLUENCY					
Animal	14.00(4.73)	14.63 (3.94)	16.25(6.18)	15.69(4.65)	.66/1, 38
"ㅅ"*	7.67(3.26)	8.50(3.44)	8.67(3.19)	10.13(4.28)	.43/1, 38

F: F-value of interaction terms

df: degree of freedom

FIQ: full scale intelligence quotient; VIQ: verbal intelligence quotient; PIQ: performance intelligence quotient; VMI: visual-motor integration.

* "ㅅ" : Korean alphabet "ㅅ" is a consonant, sound like "S".

Table 5. Results of Paired *t*-test Applied to Cognitive Function Subtest Scores

	t-value, Before and After Treatment	
	Experimental group (n=25)	Control group (n=17)
Intelligence		
FIQ	-2.47	*-1.63
VIQ	-.43	-1.25
PIQ	-3.55**	-1.79
VISUAL ORGANIZATION		
Picture completion	-2.59*	-.87
Picture arrangement	-2.83**	-.33
Object assembly	-2.41*	-2.24*
VISUOSPATIAL TEST		
VMI	-.38	-.52
Block design	-1.19	-1.59
MEMORY AND LEARNING		
BGT recall	-.84	-1.26
Hebb recurring span	-.56	-.29
Corsi recurring span	-.93	-.49
ATTENTION		
Digit span	-.12	4.83
Arithmetic	-1.01	-1.32
Hebb-digit	-3.81**	-4.39**
Corsi-digit	-1.15	-1.46
trail making A	1.2	4.46
trail making B	3.13**	2.60*
LANGUAGE AND VERBAL CONCEPT FORMATION		
Information	1.20	.70
Similarity	-.52	.18
VERBAL FLUENCY		
Animal	-3.13**	-1.09
"ㅅ"#	-2.26*	-2.54*

FIQ: full scale intelligence quotient; VIQ: verbal intelligence quotient; PIQ: performance intelligence quotient; VMI: visual-motor integration.

* p <.05 ** p < .01

#"ㅅ" : Korean alphabet "ㅅ" is a consonant, sound like "S".