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Original Articles

A Pilot Study for Developing an Assessment Scale for the Effect of Herbal Medicine in Healthy Children: Open-Label Study with *Gami-Jiwhangtang*

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Objective : While the demand for herbal medicine has increased continuously, scientific data attesting to pharmacological activity are still insufficient. One important reason, especially in child patients, is the shortage of standardized instruments for clinical research. This study was designed to develop a scale to assess the effect of herbal medicine in children.

Methods : The authors chose Gami-jiwhangtang (GJT) as a standard formulation and developed a scale, Bahn's Drug Evaluation Scale (BaDES), for this experiment. Forty-two healthy children, 7 and 8 years old, living in Seoul, Korea, volunteered to use GJT. The experimental group received GJT for 6 weeks, whereas the control group received no medicine. The children's mothers in both groups completed the BaDES on the sixth and twelfth week after GJT was commenced.

Results : The experimental group showed a significant improvement in overall physical condition and gastrointestinal function as compared with the control group.

Conclusion : These results suggest that BaDES may be a useful assessment tool for measuring the effect of herbal medicine.

Key Words: Herbal medicine, Assessment scale, *Gamijiwhangtang*, Children

Introduction

The demand for Complementary and Alternative Medicine (CAM) has grown rapidly within the past few years, creating a multibillion-dollar industry (Eisenberg et al., 1998). Recent surveys suggested that between 16.5% and 50% of the general (adult) population tried some form of CAM during the previous year (Eisenberg et al., 1993; MacLennan et al., 1996; Unutzer et al., 2000). Among CAM, the use of herbal medicine has also increased and become a global industry (Jagtenberg and Evans, 2003). According to a report by MacLennan et al. (1996), 48.5% used at least one non-medically prescribed alternative medicine, and among these respondents 9.9% used herbal medicine at least once.

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A problem that exists for most herbal medicines, however, is a lack of scientific studies establishing the presence of pharmacological activity and safety (Crone and Wise, 1998; Rey et al., 2003). Because general statements about herbal medicines are nonsensical and each formulation has to be evaluated on its own merits, it is very difficult to evaluate herbal formulations (Ernst and Pittler, 2002). A comprehensive approach and the need to consider the person as a single universe in alternative therapies also makes the concepts of standardization, quantification, generalization, and normalization problematic for both research and clinical activity as compared with conventional medicine (Spencer 2003).

While the amount of information on CAM use in adults is substantial, data pertaining to childhood populations are scarce (Ernst, 1999). Most surveys (e.g., Eisenberg et al., 1993; MacLennan et al., 1996) have excluded children. To overcome these problems, one of the urgent issues is to develop tools to assess the effect of herbal medicine in clinical practice. In oriental herbal medicine, individualized tailored prescription is needed for each patient. Within that tradition, it is almost impossible to find objective data. Therefore, the authors designed a standard herbal formulation and uniform prescription period for all subjects in order to assess an objective evaluation scale for herbal medicine in children. This study was designed as an open label trial; double blind, placebo controlled procedures were not used.

Materialsand methods

1. Subjects

Subjects consisted of 7- and 8-year old, healthy children of either sex in Seoul, Korea. Subjects were enrolled in the study after written informed consent was obtained from their parents. Following psychiatric interviews, questionnaires on developmental history, and pre-medication examinations, all children with physical or psychiatric disorders were excluded. At first, 27 children (21 boys, 6 girls) were in experiment group and 26 children (16 boys, 10 girls) were in the control group. In the experimental group, 2 subjects dropped out because the subjects resisted taking the medicine, not due to any complications of the herbal formulation. The dropout rate was 7.4%. In the control group, 9 members failed to finish the experiment (dropout rate, 34.6%). In our opinion, this high dropout rate in the control group was related with the design of the study, lack of placebo control, and the Korean culture. Because Korean students, even in the first or second grade of elementary school, are busy with burdens of extracurricular schedules, their parents did not want to repeat the same tests for their children who were obviously not taking any medicine.

After dropout, 42 subjects completed the study: 25 subjects (20 boys, 5 girls) in the experimental group and 17 subjects (10 boys, 7 girls) in the control group. Parents decided which group (experimental or control) each subject would be assigned to.

2. Herbal formulation

Gami-jiwhangtang (GJT) was used as our standard herbal formulation. GJT is employed as a kind of restorative medicine for children with developmental delay, and also for adults with renal diseases or diabetes mellitus (Cho, 1999; Lee and Park, 1996). In preclinical experiments with this formulation, GJT showed beneficial effects, as evidenced by an increase of cell proliferation in the dentate gyrus of young rats (Kim et al., 2002) and protective effects against alcohol-induced decrease in new cell formation in rat dentate gyrus (Bahn et al., 2002b).

The ingredients of this formulation were as follows: Rehmanniae Radix 16g, Dioscorae Radix 8g, Corni

Fructus 8g, Alimatis Rhizoma 6g, Moutan Cortex Radicis 6g, Holen 6g, Maximowicziae Fructus 8g, and Cervi Cornu 4g. All ingredients were obtained from the Gyungdong herbal marketplace, Seoul, Korea. These were washed, dried, ground, to which honey was, and the resulting mass was made as whan (a Korean term meant a unit of herbal formulation, tablet-like).

As no rules exist for standardizing the terminology for herbal formulations, similar terms for one formulation or same term for similar formulations can be used (Park et al., 2002). In GJT's case, Liuweidihuangtang (Bahn et al., 2002b), Liuweidihuangtang-jia-wei (Bahn et al., 2002a), and Shenqiwan (Kim et al., 2002) are same formulations as GJT, and Liu-Wei-Dihuang (Wang et al., 1998), YukMiGiHwangTang (Lee and Park, 1996), and Yukmi (Kim et al., 2000) are similar formulations. 'Gami' is Korean words and means 'addition.'

3. Examination Tools

(1) Questionnaires on demographic information and developmental history (from birth to age 6) were completed by subjects' mothers and reviewed by the authors.

(2) Physical check-ups repeated for 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.

(3) For the assessment of emotional aspects, the participants' mothers completed the Korean Personality Inventory for Children (KPI-C) (Kim et al., 1997).

(4) Bahn's Drug Evaluation Scale (BaDES) (Fig. 1), developed by the authors for this study, consisted of questions commonly raised when using this formulation, with a five-point scale for each entry. 'Marked improvement' was scored 5 and 'marked deterioration' was scored 1. This scale mainly covered physical aspects such as (a) general conditions like soundness of sleep, affliction with the common cold, "complexion in face" (a Korean term meant to capture healthfulness of one's appearance), and irritability; (b) gastrointestinal functions such as appetite, digestive power, bowel problems like constipation or diarrhea, etc, and abdominal pain; (c) specific signs or symptoms like shortness of breath, myalgia, and headache; and (d) chronic illness NOS. The total number of questions was 12.

4. Methods

Subjects in the experimental group received GJT treatment at a dose of 18 g/day (about 55 whans of GJT/day) for 6 weeks, starting on completion of the preliminary physical and psychiatric examinations. Immediately after the administration of the last dose, CBC/DC, U/A, ECG, and chest PA were carried out, and mothers completed the BaDES. Following a subsequent 6-week follow-up period, CBC/DC, U/A, ECG, chest PA, BaDES, and KPI-C were carried out again. Subjects in the control group underwent the same examination process at the same intervals without any medicine (Table 1).

5. Statistical analysis

Student's *t*-test was carried out for comparisons by group. For the reliability of BaDES, alpha coefficients were calculated. SPSS version 11.0 was employed for statistical calculations.

Results

1. Demographic factors

With one exception, no significant differences existed between the experimental and the control groups (Table

2). However, father's education within the control group was found to be significantly higher than in the herbal group (t = -2.86, p < .01).

2. Physical check-up

No significant differences in height or weight were observed between the experimental and the control groups (Table 3). No significant differences in laboratory findings (including CBC/DC, urinalysis, chest PA, and ECG results) were observed between the experimental and the control groups.

3. Personality and Emotional Aspects

No differences in the results using KPI-C were observed between the experimental and the control groups prior to administration of GJT. However, markedly fewer complaints of anxiety were made in the experimental group than in the control group (t = -2.05, p < .05) six weeks after treatment with GJT.

Assessment of Responses to Medication (Table 4)

Six weeks after commencing administration of GJT, subjects in the experimental group were able to sleep better (t = 2.40, p < .05), were less afflicted with the common cold (t= 4.94, p < .01), had better appetite (t = 2.27, p < .05), had better digestion (t = 2.76, p < .01), complained less of abdominal pain (t = 2.38, p < .05), and experienced fewer episodes of myalgia (t = 2.37, p < .05).

Some 12 weeks after starting GJT (i.e., 6 weeks after completing therapy), subjects of the experimental group scored markedly better in terms of affliction with the common cold (t = 4.79, p < .01), complexion (t = 3.00, p < .01), appetite (t = 2.99, p < .01), digestion (t = 4.37, p < .01), and stool passage (t = 2.55, p < .05).

To assess the internal consistency of the BaDES, we computed the alpha coefficient on the sixth week of treatment and found it to be 0.73.

Discussion

There were no differences in sociodemographic data between experimental and control groups, except for higher educational level of fathers in the control group. Because the families decided whether or not to use herbal medicine, it is possible that highly educated fathers may have avoided the use of herbal medicine for their children. On the other hand, several papers from North America (Eisenberg et al., 1998; Millar, 1997; Unutzer et al., 2000) reported that families of CAM or herbal medicine users had higher SES and were more highly educated than non-users in U.S. and Canada.

No significant changes in height, weight, CBC/DC, U/A, ECG, and chest PA in any of the subjects suggest that the herbal formulation had no adverse effects in this respect. Conversely, six weeks might not be enough to cause significant changes to appear. According to Bensoussan et al. (1998), Chinese herbal formulation individually tailored to the patient proved no more effective than standard Chinese herbal medicine (CHM) treatment. However, on follow-up 14 weeks after completion of treatment, only the individualized CHM treatment group maintained improvement. Therefore, it appears that choice of prescription and length of use may influence results.

On the KPI-C, only the anxiety subscale in the experimental group revealed as decrease after medication. As there are no reports of an anti-anxiety effect of GJT, this should be regarded as tentative, needing confirmation in future investigations.

At least partial improvements on BaEDS were observed in the experimental group when compared to the control group. Physically, the experimental group was less afflicted with the common cold and was reported to have a better complexion. Such findings may be related to improvement of general physical

condition or even of immunity. The experimental group also had a better appetite, digested food better, and reported improved bowel habits. Even after discontinuation of GJT, these improvements continued, suggesting that GJT improved gastrointestinal functions.

Symptoms such as 'shortness of breath,' 'headache,' or 'chronic disorder NOS' did not show significant changes. This may be because all subjects were healthy children. If they were physically ill or weak, there would have been more room for change in these areas.

Lab tests like CBC, U/A, ECG and X-ray are basic tools for evaluating physical change in clinical practice. It seems unlikely that changes would occur on these tests with herbal formulations. Changes that occurred on the BaDES, as reported by children's parents, seemed to be a more subtle effect of the herbal formulation. However, it has to be determined whether changes on BaDES were truly the effect of herbal medicine or whether they were the result of the placebo effect.

The internal consistency of the BaDES, as assessed by the alpha coefficient, was 0.73 and appears to be reasonable. The subjects' mothers completed the BaDES instead of children; if the scale was used for adults themselves, it might be more accurate.

Even though herbs are a complex form of medicine and there are insufficient data on safety, efficacy, and cost of herbs, herbal medicine is a popular treatment and is regarded by many as helpful and useful (Mills, 2002). As a result, research is required to fill the gaps in present knowledge and should have a high priority (Ernst and Pittler, 2002). At this point, it appears that the BaDES may be a sensitive clinical tool for research on the efficacy of herbal medicine in clinical practice.

We are aware that there were many limitations to this study. The limitations included (a) small sample sizes, (b) a relatively short period of treatment (compared to clinical practice in oriental medicine), (c) a lack of gender matching among the subjects, (d) an open-label design with no placebo control, (e) lack of random assignment to groups, and (f) a lack of long-term follow-up data. The fact that participants in the control group were all healthy individuals with normal school lives (and thus subject to non-experimental factors) posed an additional problem.

Conclusion

To obtain scientific clinical data with herbal medicine, it is essential to develop assessment tools. Conventional laboratory methods are unlikely to be sensitive to subtle treatment effects. The BaDES may be a useful scale for assessing the effects of herbal formulations in children.

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Name of child _____ Date of birth_____

※ Read the following list and place a check in the appropriate box

Items / Lists	Marked improvement	Some improvement	No change	Some deterioration	Marked deterioration
Soundness of sleep					
Affliction with common cold					
Complexion					
Appetite					
Abdominal pain					
Digestive power					
Bowel habit					
Shortness of breath					
Myalgia					
Headache					
Chronic illness NOS					

Figure 1. Bahn's Drug Evaluation Scale (BaDES)

Table 1. Examination Schedule

Time / Tests & Examinations	Before Treatment (Baseline)	6 weeks after commencement (Week 6)	6 weeks after completion (Week 12)
Height & Weight	X	X	X
Questionnaires on developmental history (based on the mother's account)	X		
Lab tests(CBC/DC, U/A, ECG, Chest PA)	X	X	X
KPI-C	X		X
Bahn's Drug Evaluation Scale		X	X

Note. Chest PA: Chest X-ray Posterior-Anterior View; KPI-C: Korean Personality Inventory for Children.

Table 2. Sociodemographic Factors ±mean (S.D.)

Factors \ Groups	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	x^2=1.59

** $p < .01$

Socio-Economic Status: This classification depended upon parents' judgment.

Table 3. Weight and Height Changes Following Administration of Preparation

Items \ Period	Before commencement: Mean (SD)		*t*-value	12 weeks after commencement: Mean (SD)		*t*-value
	Experimental group (n=24)	Control group (n=16)		Experimental group (n=22)	Control group (n=15)	
Weight (kg)	24.15 (5.01)	26.31 (3.45)	-1.612	5.34 (4.46)	27.63 (3.50)	-1.74
Height (cm)	123.60 (5.73)	124.25 (5.13)	-.37	124.47 (4.63)	125.86 (5.10)	-.85

Table 4. Changes in Physical Status Following Administration of Preparation.

Items \ Period	6 weeks after commencement: Mean (SD)		*t*-value	12 weeks after commencement: Mean (SD)		*t*-value
	Experimental group (n=25)	Control group (n=17)		Experimental group (n=25)	Control group (n=17)	
Soundness of sleep	3.43 (.59)	3.07 (.70)	2.40*	3.46 (.83)	3.13 (.35)	1.68
Affliction with common cold	3.76 (.70)	2.93 (.26)	4.94**	4.08 (.71)	3.13 (.51)	4.79**
Complexion	3.52 (.60)	2.93 (.49)	3.10**	3.58 (.77)	3.07 (.25)	3.00**
Irritability	3.14 (.79)	3.07 (.26)	.38	3.17 (.56)	2.93 (.25)	1.75
Appetit	4.00 (.83)	3.43 (.64)	2.27*	3.79 (.65)	3.20 (.56)	2.99**
Digestive power	3.71 (.64)	3.21 (.42)	2.76**	3.58 (.65)	3.00 (.00)	4.37**
Bowel habit	3.33 (.73)	3.07 (.47)	1.28	3.21 (.41)	2.93 (.25)	2.55*
Abdominal pain	3.21 (.42)	2.83 (.38)	2.38*	3.17 (.38)	2.92 (.28)	1.78
Shortness of Breath	3.18 (.40)	3.00 (.00)	1.49	3.18 (.40)	3.00 (.00)	1.49
Myalgia	3.21 (.42)	2.82 (.40)	2.37*	3.08 (.28)	2.92 (.28)	1.41
Headache	2.92 (.27)	2.92 (.28)	.05	2.92 (.28)	3.08 (.28)	-1.41
Chronic disorder not otherwise specified	3.09 (.30)	3.00 (.00)	1.00	3.25 (.45)	3.00 (.00)	1.91
OVERALL CHANGE	.33 (.48)	.21 (.42)	.76	.21 (.41)	.27 (.45)	-.40

* $p < .05$ ** $p < .01$

Note: Higher scores reflect greater improvements from baseline to treatment assessment.