ADVERSE EVENTS ASSESSMENT OF TRADITIONAL CHINESE HERBAL PRODUCT, GUILU ERXIAN JIAO, IN HEALTHY VOLUNTEERS

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Guilu Erxian Jiao (GEJ) is a widely used herbal product for anti-aging and treatment of degenerative joint diseases. As drug adverse events of GEJ have not been well established, this paper was designed to assess adverse events of GEJ. 96 healthy volunteers were enrolled in this study, and a randomized, placebo-controlled, double-blind clinical trial was conducted. Adherence-to-protocol design was adopted to assess the precise side effects. Analysis on laboratory data of renal function, liver function, hematological changes, immunological parameters and questionnaires about possible adverse effects after two-month medical treatment were performed. In addition, another self-report of adverse events after taking GEJ was recorded. There were no clinically significant changes of biochemical indicators of liver function, renal function and hemogram. Ratio of $CD4^+$ to $CD8^+$ lymphocyte counts reversed in the subgroup of higher GEJ dosage (300mg/day and 450mg/day) which may explain the effectiveness of GEJ for osteoarthritis. In the analysis of the questionnaire, mouth dryness was the only one adverse event and its severity seemed not relevant to GEJ dosage. Further clinical trials can be designed based on the safety profile to evaluate the effectiveness of GEJ.

Key words: Formulas of Chinese medicine, Chinese herbal product, Guilu Erxian Jiao, adverse events

Introduction

The use of traditional Chinese medicine (TCM) has been increasing rapidly in the recent years for many different diseases in the world[1-4]. In Taiwan, this trend is obvious over the past few decades. About 60 percent of Taiwanese has ever used TCM at least once in the past 6 years[5]. Less side effects and payment by National Health Insurance may contribute to the extensive use of TCM in Taiwan[5,6]. On TCM's viewpoint, due to its subtle effects, herbal products are often demanded to be used for a period of time to achieve therapeutic goal. However, the majority of current studies were put emphasis on efficacy but still

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few studies stressed on adverse drug events[3,7]. More than effectiveness, adverse drug events survey became an urgent issue to be examined with the growing use of herbal products[8].

Guilu Erxian Jiao (GEJ), also named "tortoise shell and deer antler syrup", is a well-known TCM herbal product that has been used for thousands of years and remains popular today. GEJ is commonly prescribed for anti-aging and treatment of degenerative joint[9,10]. On the TCM viewpoint, components of GEJ have both "warm" and "cold" properties and have been used to treat kidney deficiency and nourish blood, qi, ying and yang. Both qi and blood play an important role in treating joint disease at cellular level[11,12]. Nevertheless, due to the "warm" property of GEJ composition and the necessity of long-term use of GEJ, adverse effects have been concerned by TCM doctors. Moreover, the assessment of possible GEJ adverse events, such as hemogram, renal and liver function profile has not been well characterized yet[7,13,14]. The aim of this study was to evaluate the adverse events of GEJ by regularly monitoring on renal function, liver function, hematological changes, immunological parameters and analyzing questionnaires with self-report symptoms for possible adverse effects after two months of use of GEJ.

Materials and Methods

I. Subjects enrollment

This study enrolled female and male volunteers, aged from 20 to 45 years, with no clinically significant medical history, from January to October, 2006. People who had acute illness, active infection, any physical or laboratory proof of systemic diseases, history of immunodeficiency, use of immunosuppressive drugs, any treated or un-treated malignancies, neurologic abnormality, pregnancy, breast-feeding, or any herbal products allergy history, were excluded from this investigation. Subjects with abnormal findings on chemistry and hematology tests, and other conditions, which may interfere with the study result, judged by the investigator were excluded from this trial as well.

The details of this investigation were well explained to every volunteer. All participants were asked to sign informed consent after acknowledging all the instructions on the aim of the investigation, composition of GEJ, treatment duration, and evaluation methods. The protocol was approved by the Medical Ethics and Human Clinical Trial Committee of Chang Gung Memorial Hospital, Taipei, Taiwan (CGMH IRB No.95-0336B, issued date: Jan. 26, 2007), and was in accordance with the most recent version of the Declaration of Helsinki.

II. Protocol

Once eligibility to this trial was confirmed, a randomization code, regarded as subject number, was assigned to every health volunteers. On the first visit, every volunteer was randomized to one of the following groups: placebo group, group A, group B, and group C, which placebo, 150mg/day, 300mg/day, and 450mg/day of GEJ capsules were administered separately. All the participants in those four groups received five capsules containing either starch or different dosages of GEJ two times a day for 2 months and then were evaluated by TCM doctors on the visit of 4^{th} and 8^{th} week. The actual medication given to each subjects had been kept in encryption until the end of this trial and, therefore, it was masked from the investigators.

To assess the adverse effects of GEJ, a question-

naire about all possible discomfort after taking GEJ was designed to avoid omission since adverse events may be subtle. The questionnaire contained 15 symptoms (Table 1), which were all commonly presented by patients taking herbal products. Each symptom was scored on a scale from 0 to 3, with 3 representing the most severe discomfort. Any discomfort, other than questionnaire contents, was reported by participants and recorded in detail. Additionally, extensive laboratory examination including renal function, hepatic function and hemogram were checked regularly. Counts and ratio of $CD4^+$ and $CD8^+$ lymphocytes on the first and the last visit were compared as an indicator of immunomodulation. Liver and renal dysfunction was defined as more than 1.5 times of the upper limit of the average reference levels provided by laboratory of CGMH: serum aspartate aminotransferase (AST) was 34 U/L, serum alanine aminotransferase (ALT) was 36 U/L, blood urea nitrogen (BUN) was 21 mg/dL, and serum creatinine was 1.4 mg/dL.

III. Herbal preparations

GEJ capsules, prepared according to the well-documented TCM formula from the ancient book of Chinese medicine "*The Golden Mirror of Medicine*", were provided by the Chuang Song-Zong Pharmaceutical Factory, a manufacturer certified in herbal Good Manufacturing Practice (GMP) in Taiwan. The origin and quality of GEJ preparation was well controlled by the manufacturer and all GEJ capsules were made during the same period (batch number: RD-EG689601). The components of the GEJ capsules are showed in Table 2 and manufacture method of the GEJ is as followed: Carapax et Plastrum Chrysemys and Cornu Cervi were stewed for 7 days, and then Ginseng Radix Rubra and Lycii Fructus were added

Table 1. The 15 symptoms contained in the questionnaire for possible discomfort or adverse events after taking GEJ.

Drug allergy	Mouth dryness	Dizziness	Headache
Constipation	Diarrhea	Chest tightness	Palpitation
Pallor	Hot flush	Fever	Easily-sweating
Poor appetite	General malaise	Itching	

Table 2. Components of GEJ (every 250 mg of a water extract are derived from 1.42 grams of raw material).

Components			Weight (mg)
Pharmaceutical Name	Species	Plant part	
Carapax et Plastrum Chrysemys	*Pseuclemys scripta elegans* *Chrysemys scripta elegans*	Plastron	416.6
Cornu Cervi	*Rangifer tarandus*	Antler	833.3
Ginseng Radix Rubra	*Panax ginseng* C. A. Mey.	Root	75
Lycii Fructus	*Lycium barbarum* L.	Fruit	91.7*

*Traditionally, the ratio between 4 components is about 5:10:1:2 (ordered as list); GEJ capsule in this study has less Lycii Fructus.

into the mixture of Carapax et Plastrum Chrysemys and Cornu Cervi. The concentrate is extracted. GEJ capsule is made of dried mixture of extracted concentrate and excipient in fixed proportion. This manufacture method was slightly different from traditional method: Ginseng Radix Rubra and Lycii Fructus were stewed separately but not added into mixture according to the classics. Therefore, high-performance liquid chromatography (HPLC) was also used to ensure quality of GEJ components. Placebo capsules were made with the same appearance, packaging, and quantity as the GEJ capsules. The labels of all capsules were well encrypted so that no one could ascertain the components of the capsules when taking the capsules until the samples were decrypted at the end of this investigation.

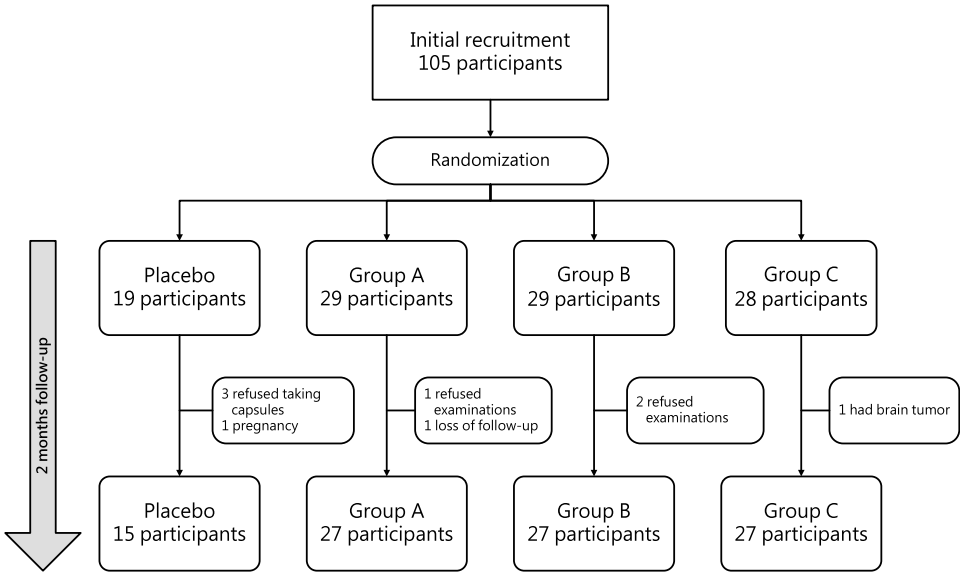

Fig. 1. The progress of participants through this study.

Table 3. The descriptive statistics for the participants of the four groups.

	Placebo	Group A	Group B	Group C	*p* value
Sex					0.162
Male	6	4	11	9	
Female	9	23	11	18	
Total	15	27	27	27	
Age					0.562
Maximum	45	44	43	45	
Minimum	24	25	20	21	
Median	35	32	33	33	
Mean	34.2	32.7	31.7	33.5	
SD	6.4	5.1	6.3	6.2	

SD, standard deviation

IV. Statistical analysis

SPSS package, version 12.0, was used to analyze data. Results of laboratory assays were compared between before and after using GEJ by paired Student *t*-test. Also, one way analysis of variance was used to compare the continuous variables between 4 groups. For ordinal data obtained from questionnaire, Kruskall-Wallis test was used to analyze the differences of symptom severity between 4 groups, and Bonferroni method was used for post hoc test. Also, Wilcoxon signed ranks test was used for assessment of symptom severity within each group. *P-value* less than 0.05 was thought as a significant result. All results were analyzed according to adherence-to-protocol design.

Results

There were 105 people enrolled in this study initially, with 29 men and 67 women eventually completing the whole study. Their ages ranged from 20 to 45 years old. At the end of study, 96 participants remained; 3 experiment groups had 81 participants and control group had 15 participants. Reasons for the 9 participants who withdrew from the study were listed as following: 3 were unwilling to receive laboratory examination, 3 were unwilling to be enrolled in this study due to reluctant acceptance of herbal preparations after taking few capsules of GEJ, one for pregnancy, one for failure to return for no known reason, and one for a brain tumor found at the follow-up clinical visit. The progress of participants through this study was showed as Fig. 1. Distribution of age and sex among four groups were similar. (Table 3)

Laboratory assays showed higher platelet count in Group A and decreased BUN in Group B after taking GEJ for 2 months ($p < 0.05$); however, the level

Table 4. The changes of biochemical and hematological data comparing before and after taking GEJ between four groups.

	Placebo				Group A				Group B				Group C				P-value	
	Before		After		Before		After		Before		After		Before		After		Before	After
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD		
WBC	6.8	1.5	6.9	1.8	6.5	1.5	6.5	1.2	6.5	1.4	6.8	1.4	6.6	1.5	6.4	1.4	0.564	0.444
Hb	13.7	1.5	13.5	1.7	13.3	1.7	13.2	1.7	13.5	1.5	13.4	1.6	13.9	1.5	13.9	1.7	0.567	0.505
PLT	256.3	49.3	257.3	54.6	259.9	52.7	271.5*	58.0	251.6	54.0	256.6	58.8	254.8	81.7	254.5	68.9	0.951	0.796
BUN	11.6	3.2	11.4	2.7	10.4	2.4	10.1	2.7	11.4	3.2	9.9*	3.1	10.7	3.0	10.6	2.9	0.376	0.436
Cr	0.8	0.2	0.9	0.1	0.7	0.2	0.74	0.2	0.8	0.2	0.9	0.2	0.8	0.2	0.8	0.3	0.188	0.121
AST	20.0	7.3	19.8	6.7	20.4	5.9	19.6	5.8	20.4	7.3	7.3	11.4	19.7	5.6	20.3	6.8	0.961	0.612
ALT	19.3	17.7	20.1	18.6	19.11	10.9	17.6	10.7	20.4	14.3	24.6	24.1	18.3	10.1	20.5	14.7	0.935	0.570

WBC: white blood cell ($10^3/mm^3$); Hb: hemoglobin (g/dL); PLT: platelet ($10^3/mm^3$); BUN: blood urea nitrogen (mg/dL); Cr: Creatinine (mg/dL); AST: aspartate aminotransferase (IU/L); ALT: Alanine Aminotransferase (IU/L); SD: standard deviation; Before: before taking GEJ; After: 2 months after taking GEJ

* $p < 0.05$

of BUN and platelet counts were still within normal limits. The other parameters of laboratory assays had no statistically significant changes among four groups before and after treatment (Table 4). In the immunomodulation assay, the $CD4^+$ T lymphocyte percentage and the ratio of $CD4^+$ to $CD8^+$ T lymphocytes decreased significantly in group B and C (Fig. 2 and 3). There were no changes in $CD8^+$ T lymphocyte percentage among all the groups. $CD4^+$ T lymphocyte percentage and the ratio of $CD4^+$ to $CD8^+$ T lymphocytes were no changed in group A and the placebo group (Table 5).

For the assay of clinical symptoms, there were no significant differences between 4 groups when comparing with baseline separately. Analyzing within group symptom severity showed dizziness, headache, chest tightness, palpitation, flushing, profuse-sweating, diarrhea, and general malaise improved; while mouth dryness became worse after taking GEJ in group A (Table 6). In addition to questionnaire, one abdominal fullness event was reported in group A, which was a minor, expected and perhaps study-related events.

Discussion

Overall, there was no significant influence on hemogram, liver or renal function after taking GEJ for two months. This may indicate that GEJ had no harmful impact on the patient's basic biochemical profile that is the most common indicator for the clinical evaluation of health conditions. On the other hand, no prominent changes within the biochemical profile ensured that using GEJ may not interfere with regular biochemical data in certain diseased populations such as those with liver or renal function impairment. Also, this result may imply that it is not necessary to adjust the dosage of GEJ according to liver or renal function.

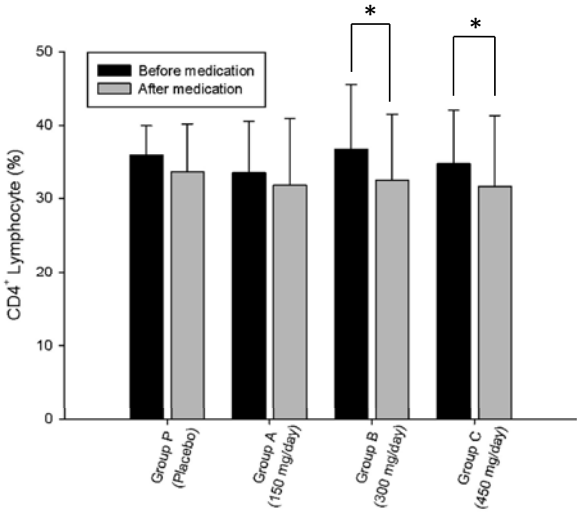

Fig. 2. Comparison of $CD4^+$ T lymphocyte count before and after medication. $CD4^+$ T lymphocyte counts decreased in group B and group C after using GEJ for 2 months.
*** $p < 0.05$**

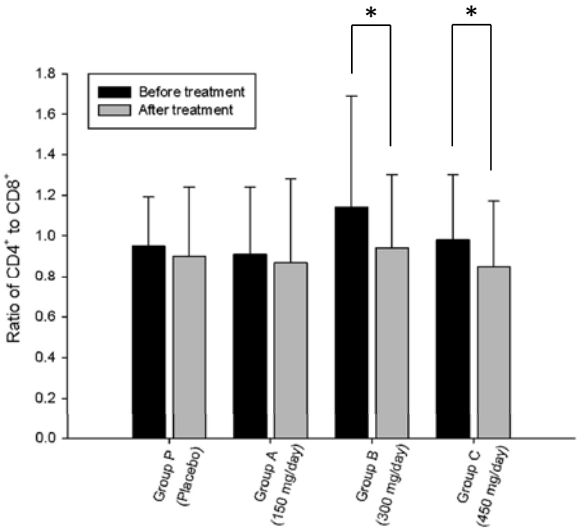

Fig. 3. Comparison of $CD4^+/CD8^+$ T lymphocyte ratio before and after medication. Ratio reversed significantly in group B and group C after using GEJ for 2 months.
*** $p < 0.05$**

On the analysis of possible adverse effects, certain discomforts, such as abdominal fullness, constipation, diarrhea or nausea, which were commonly concerned

Table 5. Comparison of $CD4^+$ and $CD8^+$ T lymphocyte count and ratio before and after taking GEJ between four groups.

	Placebo				Group A				Group B				Group C				P-value	
	Before		After		Before		After		Before		After		Before		After		Before	After
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD		
CD4	35.9	6.6	33.6	6.6	33.5	7.1	31.8	9.2	36.6	8.9	32.4*	9.2	34.7	7.4	31.6*	9.7	0.589	0.980
CD8	39.4	7.7	39.9	7.7	38.8	7.1	39.7	8.2	35.0	6.9	36.0	6.8	37.3	7.8	38.3	6.7	0.183	0.166
ratio	0.91	0.3	0.84	0.3	0.86	0.3	0.80	0.4	1.04	0.55	0.94*	0.36	0.93	0.32	0.83*	0.32	0.192	0.817

*p *value* < 0.05 (comparison within groups)

Table 6. Comparison of adverse events before and after taking GEJ.

	Groups							
	Placebo	p-value	Group A	p-value	Group B	p-value	Group C	p-value
Symptoms Ameliorated								
	Dizziness	0.046	Dizziness	0.007	Headache	0.000	Dizziness	0.005
	Headache	0.034	Chest tightness	0.046	Diarrhea	0.000	Headache	0.001
	Chest tightness	0.046	Palpitation	0.012	Chest tightness	0.020	Diarrhea	0.008
	Palpitation	0.046	Hot flush	0.013			Chest tightness	0.009
	Hot flush	0.025					Palpitation	0.025
	Easily-sweating	0.014					Hot flush	0.003
							Easily-sweating	0.011
							General malaise	0.007
Symptoms Deteriorated								
			Mouth dryness	0.011				

by people taking herbal products[15], were not found after taking GEJ for 2 months. Nevertheless, mouth dryness, one of the most common adverse effects of all Chinese herbal products with "warm" property, seemed to be the only symptom deteriorated after taking GEJ. The severity was not related to dosage, since it was only precipitated in group A.

Difference between current GEJ capsule and traditional GEJ may possibly contribute to occurrence of mouth dryness. Less Lycii Fructus in GEJ capsule may precipitate mouth dryness. In TCM classics, such as the *Compendium of Materia Medica*, herbal products with "warm" property should be warned against the possibility of promoting mouth dryness, which may be a result from increasing the metabolic rate or other unknown mechanisms of body fluid depletion, especially used on person with "warm" constitution. Among the components of GEJ, Cornu Cervi and Ginseng Radix Rubra both have "warm" property, especially the former one.

The adverse effect on "warm" constitution population was not assessed since subgroup analysis of participants with "warm" constitution in this study was not feasible due to limited case number. Also, constitution surveillance was not done before recruitment. This may overestimate the incidence of mouth dryness since clinical TCM doctors would use GEJ discreetly when patient was with warm constitution. Therefore, it is suggested that TCM practitioners should remind patients of mouth dryness when using GEJ, especially the people supposed to have "warm" constitution. Besides, dosage adjustments, or even discontinuation of GEJ may be considered if mouth dryness is severe.

As a part of adverse events assessment, the effect of GEJ on immunomodulation was checked. The results showed higher doses of GEJ caused $CD4^+$ T lymphocytes to decrease more prominently. Many reports have demonstrated that a number of Chinese herbal products exert diverse effects on allergic diseases via different immunomodulation pathway. Regulating the function of T lymphocytes and the ratio between lymphocyte subgroups may be one of the most important mechanisms[16]. Besides, prior report showed that $CD4^+$ T lymphocytes increase prominently in the sub-lining layer of the synovium in patients with osteoarthritis compared with normal subjects[17]. The fact that GEJ reversed the ratio of $CD4^+$ to $CD8^+$ lymphocyte counts may explain the effectiveness of GEJ for osteoarthritis, which may be the most common indication for GEJ in Taiwan. Furthermore, Lycii Fructus and *Panax ginseng*, two of the four components in GEJ, are reported to have immunomodulation effects by inducing Th1, natural killer cells, macrophages, and reducing free radicals[18-21]. Based on these findings, one may assume that the mechanism of GEJ to treat osteoarthritis might be through suppressing $CD4^+$ T lymphocytes or reversing the ratio of $CD4^+$ lymphocytes to $CD8^+$ lymphocytes. Nevertheless, GEJ was once reported to have effect of suppressing splenic T-lymphocyte[9]. Therefore, GEJ may possibly have ability of biphasic modulation of T-lymphocyte function. Further studies examining the exact effect and the mechanism of action of GEJ are still needed.

Conclusion

There were no significant impacts on renal function, hepatic function, or hemogram after taking GEJ (provided by Chuang Song-Zong Pharmaceutical Factory) for 2 months. Also, no serious adverse

events were found, except mouth dryness. The facts about decreasing $CD4^+$ lymphocyte count and reversal in ratio of $CD4^+$ and $CD8^+$ lymphocyte were recognized. Further researches could be conducted on the basis of this adverse events assessment and patient's constitution surveillance should be done before GEJ administration to avoid adverse events, such as mouth dryness.

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中藥龜鹿二仙膠在健康族群的臨床不良反應評估

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龜鹿二仙膠為臨床重要方劑，已有千年歷史，常用於退化性關節疾病與對抗老化，亦包含於台灣全民健保給付，然而，其安全性卻尚未經過臨床試驗檢驗。本試驗納入96名健康受試者，隨機分配成四組，包含安慰劑與三種不同劑量的龜鹿二仙膠膠囊，分別為一天150毫克、300毫克與450毫克，進行兩個月的隨機雙盲臨床試驗。期間以血相變化、肝腎功能變化、症狀問卷進行客觀與主觀的評估，並測試$CD4^+$和$CD8^+$T淋巴球之個數與比例，監測對於免疫系統調節之影響。兩個月持續服用後，血相、肝腎功能方面並沒有明顯影響，症狀方面，口乾是唯一有意義的不良反應。$CD4^+$T淋巴球與$CD4^+/CD8^+$T淋巴球之比例亦呈現有意義的變化；在較高劑量組（300毫克/天與450毫克/天），$CD4^+$數目下降，且$CD4^+/CD8^+$比例反轉，此與其可用於治療退化性關節炎的機轉相關。龜鹿二仙膠在使用上需注意可能的口乾症狀，後續之療效試驗亦可續行於此安全性調查之結果。

關鍵字：中草藥、方劑、龜鹿二仙膠、藥物不良反應

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