

Clinical Observations

Clinical Observations on the Dose-effect Relationship of Gegen Qin Lian Decoction (葛根芩连汤) on 54 Out-patients with Type 2 Diabetes

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Objective: To observe the therapeutic effect of different dosages of Gegen Qin Lian Decoction (葛根芩连汤) on type 2 diabetic patients.

Methods: Fifty-four type 2 diabetic patients from low dosage group (20 cases), medium dosage group (19 cases) and high dosage group (15 cases) were treated with different dosage of Gegen Qin Lian Decoction for 12 weeks. Fasting blood-glucose (FBG), postprandial blood sugar (PBG) and Hemoglobin A1c (HbA1c) were determined before and after treatment.

Results: With the increase of dosage, the overall effective rate of glycaemic control increased, and FBG, PBG, HbA1c decreased. The overall effective rate of blood glucose control of high dosage, medium dosage and low dosage group were 80%, 47%, 30% respectively, and there were significant differences between high dosage group and low dosage group. The decrease of FBG, PBG and HbA1c of high dosage showed significant differences from low dosage too. These data was analyzed by trend χ^2 test and covariance analysis.

Conclusion: The result indicated that different dosage of Gegen Qin Lian Decoction has dose-effect relationship in reducing HbA1c and FBG.

Keywords: *Gegen Qin Lian Decoction; dose-effect relationship; type2 diabetes*

Generally, most of TCM physicians believed that diabetes is caused by yin deficiency and dry heat. However, some patients showed some symptoms of damp-heat syndrome. Gegen Qin Lian Decoction (葛根芩连汤) which was one prescription of Treatise on Febrile Diseases is mainly used to treat diarrhea caused by internal heat and dysfunction of large intestine. Physicians in the Qing Dynasty (1616-1911 AD) used the compound recipe to treat epidemic febrile diseases in four seasons. In this study, different dosages of Gegen Qin Lian Decoction were used to treat 54 type 2 diabetic patients with damp-heat syndrome of spleen from June 2009 to April 2010. The study is reported as the followings.

METHODS

General Data

Subjects were outpatients of endocrine department, Guang'anmen Hospital, China Academy of Chinese Medical Sciences.

Standard of Diagnosis

1) Diabetes-diagnosing Standard published by World Health Organization (WHO) in 1999.¹

2) TCM diabetes-diagnosing Standard in Guideline for Clinical Research into New Chinese Drugs printed in 2002.² Patients suffered from the syndrome of damp-heat in the spleen.

Inclusion Criteria

The authors included patients of both genders with type 2 diabetes and damp-heat syndrome of spleen according to TCM syndrome differentiation, whose age ≤ 75 years, and FBG levels < 20 mmol/L, who voluntarily joined the clinical observation and could persisted in taking medicine for 12 weeks.

Exclusion Criteria

1) Patients whose age > 75 years. 2) Women who were in pregnancy or in lactation. 3) Patients who always changed glucose-reducing medicine and insulin. 4) Patients who had dysfunction of the liver and kidney. 5) Patients who had hypertension, coronary heart disease and other severe primary diseases. 6) In the last month, patients who had ketoacidosis, lactic acidosis, hyperosmotic coma and other acute complications of diabetes as well as infection. 7) Patients who were allergic to ingredients of Chinese drugs. 8) Patients who were unwilling to cooperate (unable to control the diet and take drug according to regulations, thus influencing the therapeutic effect), and patients suffered from mental disease.

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Intervention

The recipe in low dosage group consisted of Ge Gen (Radix Puerariae) 24 g, Huang Qin (Radix Scutellariae) 9 g, Huang Lian (Rhizoma Coptidis) 9 g, Zhi Gan Cao (Radix Glycyrrhizae) 6 g and Gan Jiang (Rhizoma Zingiberis) 1.5 g. The recipe in medium dosage group consisted of Ge Gen (Radix Puerariae) 72 g, Huang Qin (Radix Scutellariae) 27 g, Huang Lian (Rhizoma Coptidis) 27 g, Zhi Gan Cao (Radix Glycyrrhizae) 18 g and Gan Jiang (Rhizoma Zingiberis) 4.5 g. The recipe in high dosage group consisted of Ge Gen (Radix Puerariae) 120 g, Huang Qin (Radix Scutellariae) 45 g, Huang Lian (Rhizoma Coptidis) 45 g, Zhi Gan Cao (Radix Glycyrrhizae) 30 g and Gan Jiang (Rhizoma Zingiberis) 7.5 g. Chao Zao Ren (Fructus Ziziphi Jujubae) was added for insomnia. Jiu Da Huang (Radix et Rhizoma Rhei) was added for constipation. Xia Ku Cao (Spika Prunellae) and Gou Teng (Rumulus Uncariaecum Uncis) were added for hyperactivity of liver-yang. Hong Qu (Semen Oryzae cum Monasco) was added for high blood lipid. Wei Ling Xian (Radix Clematidis) was added for high uric acid. The decoction was orally taken, one dose a day, in the morning and in the evening on an empty stomach for 12 weeks as a course of treatment.

Measurements and Outcomes

HbA1c, FBG and PBG, the liver and kidney function changes, some symptoms were determined before and after the treatment. The adverse events were recorded to judge their relations with the drugs.

Statistical Analysis

One-way analysis of variance (ANOVA) was employed to compare the background characteristics of three groups. The Cochran-Armitage trend test was used to evaluate the overall effective rate of glycaemic control differences of three groups, and covariance analysis was used to evaluate the FBG, PBG and HbA1c fall of three groups.

RESULTS

Baseline Data

There were no statistical differences ($P>0.05$) with respect to baseline features like gender, age and course of diabetes (Table 1).

Table 1. Clinical characteristics at baseline of 3 dosages groups of type 2 diabetic patients ($\bar{x} \pm s$)

Group	Cases	Gender male/female	Age (years)	Course of disease(years)
High dosage group	15	9/6	54.4±12.3	7.9±5.4
Medium dosage group	19	11/8	52.3±11.4	7.4±5.4
Low dosage group	20	13/7	53.3±7.2	7.3±5.8

The Overall Effective Rate of Glycaemic Control

When the decrease percentage of FBG and PBG $\geq 20\%$ of those before treatment or the decrease percentage of HbA1c $\geq 10\%$ of that before treatment, the case was thought as an effective case, and other else was thought as an ineffective case. The overall effective rate of high dosage group, medium dosage group and low dosage group were 80% (cases=20), 47% (cases=19) and 33% (cases=15) respectively. The Cochran-Armitage trend test is used for analyzing the differences of three groups. The value of χ^2 test was 7.781, and $P=0.005$, which indicate that with the increase of the dosage, the overall effective rate of glycaemic control on type 2 diabetic patients by Gegen Qin Lian Decoction increase (Table 2).

Table 2. The overall effective rate of glycaemic control of different dosages of Gegen Qin Lian Decoction on type 2 diabetic patients

Group	Effective cases	Ineffective cases	Overall Effective rate (%)
High dosage group	16	4	80
Medium dosage group	9	10	47
Low dosage group	5	10	33

The Decrease of HbA1c

Through covariance analysis, the HbA1c decrease of three groups before and after treatment were analyzed, $F=33.61$ and $P<0.001$, which showed remarkable differences. There was significant difference between the high dosage group and low dosage group, but only decrease trend between the medium dosage group and the low dosage group and between the high dosage group and the medium dosage group, indicating that high dosage has good effect on controlling HbA1c and with the decrease of the dosage, the effect decreases (Table 3, Figure 1).

Table 3. Comparison of the decrease of HbA1c (%) among three groups

Group	Cases	HbA1c (%) initial value	HbA1c (%) decrease
High dosage	18	9.20±1.84	1.79±0.11
Medium dosage	15	8.33±1.59	0.66±0.11
Low dosage	14	7.88±2.81	0.12±0.07 [▲]

Note: [▲] $P<0.05$ as compared with the datum in high dosage group.

Through covariance analysis which taking the initial value as the covariates, the FBG and PBG decrease of three groups before and after treatment were analyzed, $F=9.86$, $P<0.001$ and $F=19.15$, $P<0.001$ respectively. There was significant difference between the high dosage group and low dosage group, but no statistical difference

between the medium dosage group and the low dosage group and between the high dosage group and the medium dosage group. The results indicated that Gegen

Qin Lian Decoction had good dose-effect relationship on controlling FBG and PBG. With the decrease of the dosages, its effect reduced (Table 4).

Table 4. Comparison of the decrease of FBG and PBG

Group	FPG			PBG		
	Cases	Initial value (mmol.L ⁻¹)	Difference (mmol.L ⁻¹)	Cases	Initial value (mmol.L ⁻¹)	Difference (mmol.L ⁻¹)
High dosage	19	11.21±3.21	3.20±0.19	12	14.81±5.36	4.26±0.44
Medium dosage	19	9.82±2.17	1.06±0.13	15	14.89±4.14	2.58±0.36
Low dosage	14	8.75±4.92	0.16±0.15 [▲]	13	13.35±5.41	0.72±0.31 [▲]

Note: [▲]P<0.05 as compared with the datum in high dosage group.

Adverse Reaction

During the treatment period, one patient in high dosage group had stomachache, which disappeared when the decoction was taken after meal. One patient had constipation in the medium dosage group. No significant changes in hepatic and renal function before and after treatment in the 3 groups were found.

TYPICAL CASE

A male patient, 21 years old, was diagnosed as type 2 diabetes in Xuanwu Hospital in September 2009, with FBG 14.2 mmol/L. He was treated with Metformin for 2 months. His first visit was on November 25, 2009, the symptoms were dry mouth, thirst, drinking much more water, easy hunger, lassitude, dysphoria heat, night urination for 2–3 times every night. The weight loss was 15 kg in 2 month. The tongue was fat and the fur was yellow-white thick greasy. His body height was 188 cm, and his body weight was 103 kg. FBG was 10.6 mmol/L,

HbA1c was 8.3%, TG was 1.79 mmol/L, CHO was 5.85 mmol/L, HDL-C was 1.04 mmol/L, LDL-C was 4.35 mmol/L, HCRP was 5.88 mol/L, 0 h, 0.5 h and 2 h insulin in blood sereum were 89.3 pmol/L, 456.3 pmol/L and 32.6 pmol/L respectively; 0 h, 0.5 h and 2 h C peptide in blood sereum were 0.56 µg/L, 2.33 µg/L and 2.33 µg/L respectively, at the same time, 0 h, 0.5 h and 2 h blood glucose were 8.88 mmol/L, 15.19 mmol/L, and 14.80 mmol/L. From the respect of TCM, he was diagnosed as syndrome of damp-heat in the spleen and retention of phlegm and treated with clearing away heat, removing dampness and resolving phlegm and turbid. The recipe consisted of Ge Gen (Radix Puerariae) 120 g, Huang Qin (Radix Scutellariae) 45 g, Huang Lian (Rhizoma Coptidis) 45 g, Zhi Gan Cao (Radix Glycyrrhizae) 18g, Gan Jiang (Rhizoma Zingiberis) 7.5g, Sheng Shan Zha (Fructus Crataegi) 30 g, Hong Qu (Semen Orysa cum Monasco) 15 g and Wu Wei Zi (Fructus Schisandrae) 15 g. The result of treatment was shown as follows.

Table 5. The symptoms and indexes of different visit

Items	First visit	Second visit	Third visit	Fourth visit
Visiting time	0 month	One month	Two months	Three months
FBG (mmol/L)	10.6	9.0	9.1	7.4
2hPG (mmol/L)	14.8	12.6	11.6	9.3
HbA1c%	8.3	7.8	7.5	6.5
Hepatic function	No abnormality	No abnormality	No abnormality	No abnormality
Symptoms	Thirst, drinking much water, easy hunger, lassitude, dysphoria heat, night urination for 2–3 times every night	Alleviated thirst, lassitude relieved by 60%, no dysphoria heat, no night urination	Thirst, spontaneous sweat	thirst and spontaneous sweat disappeared
Changes in drug	See the recipe	Wu Wei Zi, Hong Qu and Shan Zha removed, Hua Shi (Talcum) 30 g added (packed separately)	Hong Qu 6 g added	-

Dosage of Western medicine were unchanged

DISCUSSION

Gegen Qin Lian Decoction originating from Treatise on Febrile Diseases written by ZHANG Zhong-jing is used

to treat diarrhea and dysentery caused by damp-heat. This classic prescription used to treat acute diarrhea consisting of Ge Gen (Radix Puerariae) 0.5 Jin, Gan Cao

(Radix Glycyrrhizae) 2 Liang, Zhi Huang Qin (Radix Scutellariae) 2 Liang and Huang Lian (Rhizoma Coptidis) 3 Liang. With the medical development, This prescription has been widely used to treat many new diseases. In this recipe, Ge Gen mainly clearing away heat from Yangming Channel, generating fluid and moistening dryness, which often was used by physicians from past dynasties to treat wasting-thirst. Huang Qin and Huang Lian were a pair of drugs for clearing away heat of excess type from the lung and stomach, which could remove glucotoxin from the blood. Huang Lian which could clear away heat, removing dampness and eliminating toxin was thought by Liu He-jian as a holy drug to treat wasting-thirst in the Jin and Yuan Period. Modern pharmacological research had confirmed that Ge Gen, Huang Qin and Huang Lian had definite effect of controlling blood glucose.

People still argued about the dosage in the Treatise on Febrile Diseases. How many grams on earth that one Liang in the book of the Treatise on Febrile Diseases amount to? 1.6, 3, 6-9, 13.92 or 15.625g.⁴⁻⁸ In 1983, Professor KE Xue-fan studied the conversion relationship of the drug dosage both East Han Dynasty (25-220 AD) and present time. According to the literature, drug weight, modern pharmacological research and clinical practice, the authors thought one Liang in ZHANG Zhong-jing's prescription as 15 g at present. In this study, one Liang was thought as 3 g, 9 g and 15 g in 3 groups respectively from low, medium and high dosage, to observe the effect of Gegen Qin Lian Decoction on type 2 diabetic patients with syndrome of damp-heat in the spleen. To avoid the stomach impairment by Huang Qin and Huang Lian, fixed percentage of dry ginger were added in each group respectively.

The result indicated that every dosage group could control the blood glucose in some extent. High dosage

group showed best effect, and then followed by the medium dosage group and the low dosage group. The dose-effect relationship was obvious. Due to uneven initial value of FBG, PBG and HbA1c in three groups, the Cochran-Armitage trend test was used to evaluate the overall effective rate of glycaemic control differences of three groups, and covariance analysis was used to evaluate the FBG, PBG and HbA1c decrease of three groups. The small sample size and limited treatment course were the inadequate point of this study. For further deep study, sample sizes should be enlarged and stricter research design should be made to elaborate the dose-effect relationship and the mechanism of Gegen Qin Lian Decoction on treating type 2 diabetes.

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