Original Research Article

Effect and safety of combined Gegen Qinlian decoction/metformin in the treatment of diabetes mellitus in patients, and its influence on serum C peptide and glycosylated hemoglobin

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Abstract

Purpose: To investigate the clinical efficacy and safety of combined Gegen Qinlian decoction/metformin in the treatment of diabetes mellitus (DM), and its influence on serum C peptide and glycosylated hemoglobin (HbAlc).

Methods: One hundred and eighty-six DM patients who received treatment in Tangshan Gongren Hospital, Tangshan City, China from July 2018 to November 2019 were randomly assigned to group X (n = 93) and group Y (n = 93). Group Y was given metformin, while X received a combination of Gegen Qinlian decoction and metformin. Total effectiveness, incidence of adverse reactions, blood glucose, TCM syndrome scores, as well as serum C peptide and HbAlc were determined and compared between the two groups.

Results: Compared with group Y, group X had significantly higher treatment effectiveness (p < 0.05), lower incidence of adverse reactions (p < 0.05), significantly lower levels of blood glucose and TCM syndrome score after treatment (p < 0.001), but significantly higher serum C-peptide levels (p < 0.001) and lower levels of HbAlc.

Conclusion: the combination of Gegen Qinlian decoction and metformin produces a good anti-diabetic efficacy, with a lower incidence of adverse reactions in patients. Therefore, the combined therapy has potentials for application in clinical practice, but further clinical trials are required.

Keywords: Serum C peptide, Glycosylated hemoglobin (HbAlc), Gegen Qinlian Decoction

INTRODUCTION

Patients with diabetes mellitus (DM) present with abnormal blood glucose and long-term organ damage, leading to cardiovascular diseases and increasing the disease-associated burden [1-3]. Therefore, early diagnosis and treatment should be carried out to strictly control the occurrence of DM. At present, blood biochemical tests are often applied to diagnose and treat DM in clinical practice, with serum C peptide and glycosylated hemoglobin (HbAlc) as common diagnostic markers [4-7]. Serum C peptide shows the frequency of insulinogenesis, while HbAlc is
often applied in the control and monitoring of DM. Indeed, HbA1c is positively correlated with blood glucose concentration and reflects the glucose level of the patient. The combined detection of serum C peptide and HbA1c is beneficial in the diagnosis and treatment of DM [8-10]. Metformin, a popular drug for treatment of DM, inhibits the rate of absorption of glucose in the gastrointestinal tract while accelerating the absorption of blood glucose in peripheral tissues. However, metformin has limited application because it often causes adverse reactions.

In recent years, with more understanding of traditional Chinese medicine (TCM) treatment, some scholars have found that Gegen Cenlian decoction effectively controls DM. Salvia miltiorrhiza, coptis and other drugs in Gegen Cenlian decoction produce positive effects of promoting blood circulation, removing blood stasis, clearing heat and relieving dryness. This study was carried out to investigate the clinical effect and safety of combined use of Gegen Qinlian decoction and metformin in the treatment of DM after the combined measurement of serum C peptide and HbA1c.

METHODS

General profiles of patients

One hundred and eighty-six DM patients treated in Tangshan Gongren Hospital, Tangshan City, China from July 2018 to November 2019 were randomly assigned to group X (n = 93) and group Y (n = 93). Group X had 49 males and 44 females, with a mean age of 65.19 ± 20.81 years, disease course of 4 - 10 years, and mean course of 7.68 ± 2.32 years. Group Y had 48 males and 45 females, with a mean age of 66.19 ± 20.81 years, disease course of 5 - 11 years, and mean course of 7.68 ± 3.32 years. There were no statistically significant differences in general profile between the two groups (p > 0.05). The study was approved by the ethics committee of Tangshan Gongren Hospital (approval no. 20180554), and performed in line with the guidelines of the Declaration of Helsinki [11]. Patients and/or guardians signed informed consent.

Inclusion criteria

Patients in the following categories were included in this study: (1) those with type 2 DM after examination [12], and (2) patients who had no cognitive dysfunction, and could cooperate with treatment and follow-up.

Exclusion criteria

Patients in the following categories were excluded: (1) patients who had mental problems or were unable to communicate with others; (2) patients suffering from hypertension, pancreatitis, infections, malignant tumors or major organ dysfunction, and (3) patients who were allergic to the drugs and examinations used in the study. Signed informed consent was obtained from all subjects or members of their families after the aim and protocol of the research were explained to them.

Treatments

Both groups received conventional treatment, but Y was given metformin, while X received a combination of Gegen Qinlian decoction and metformin. The treatment lasted for 12 weeks. In conventional treatment, the patients were given dietary guidance, exercise intervention, strict control of their body weights and close monitoring of their blood glucose. Metformin (0.5 g; Youcare Pharmaceutical Group Co. Ltd; NMPA approval no.: H20051289) was administered orally three times a day. The Gegen Qinlian decoction prescription mainly comprised 30 g of Pueraria montana var. lobata, 10 g of coptis, 10 g of Scutellaria baicalensis, and 6 g of radix Glycyrrhizae preparata. If patients had abnormal sweating, calcined dragon bone and light wheat were added. In the presence of dry stool, dry mouth and bad breath, radix pseudostellariae, radix ophiopogonis, Schisandra chinensis and Polygonum cuspidatum were included. If patients could not sleep at night, spina date seed and Polygala tenuifolia were added. The drugs were soaked in 500 mL of water and decocted, and 200 mL of extract was administered. The patients took the decoction before meals in the morning and evening, twice a day.

Evaluation of parameters/indices

Serum C-peptide

Following an overnight fast, 5 mL of blood was taken from the cubital vein of each subject after admission and at 2 h after a meal. After treatment, the blood obtained was subjected assay of serum C-peptide using an automatic chemiluminescence immunoassay analyzer with matching reagents (Cobase 411 Electrochemiluminescence Analyzer; NMPA certificate no. 2013402843) and operated strictly according to the kit instructions. The test results were used to diagnose the patients’ condition. Serum C
peptide levels were compared before and after treatment.

**HbAlc and blood glucose**

Following overnight fast, blood samples (5-mL) were obtained as before. After treatment, blood levels of HbAlc and glucose were determined with an automatic biochemical analyzer using matching reagents (Tai’an Kangyu Medical Device Co. Ltd; Shandong Food and Drug Administration no. 20142400498). At the same time, the fasting blood sugar (FBS) and 2-h postprandial blood glucose (2 h PBG) of patients were determined. Levels of HbAlc were compared before and after treatment. In addition, FBG and 2-h PBG levels were compared after treatment.

**Treatment effectiveness/efficacy**

If the patients’ symptoms disappeared, and FBG and 2-h PBG returned to normal range or decreased by more than 10 %, the treatment was markedly effective. If the symptoms were relieved, and FBG and 2h PBG decreased by 5 %, the treatment was regarded as effective. Failure to meet the above criteria meant that the treatment was ineffective [13].

\[
TE (%) = \frac{ME}{T} \times 100 \quad \text{.............. (1)}
\]

where: \(TE = \) Total effectiveness; \(ME = \) number of markedly effective cases; \(E = \) number of effective treatments, and \(T = \) total population of subjects.

**Incidence of adverse reactions**

Adverse reactions included nausea, vomiting, diarrhea, headache and hypoglycemia. The number of patients with adverse reactions was noted.

**TCM syndrome score**

The TCM syndrome score scale was adopted to evaluate the TCM syndrome score after treatment [14,15].

**Statistical analysis**

Data processing was done using SPSS 23.0 package, while GraphPad Prism 7 was used for preparation of graphs. Measurement results are expressed as mean ± SD, and were analyzed using ANOVA with repeated measurement data, including total effectiveness, incidence of adverse reactions, FBG, 2 h PBG, serum C peptide and HbAlc. Enumeration data, i.e., total treatment effectiveness and incidence of adverse reactions were analyzed using chi squared test. Differences were considered statistically significant at \(p < 0.05\).

**RESULTS**

**Clinical effectiveness/efficacy**

Treatment effectiveness was significantly higher in group X than in group Y (\(p < 0.05\); Table 1).

**Incidence of adverse reactions**

There were fewer incidence of adverse side effects in group X (2.15 %) than in group Y (15.05 %, \(p < 0.05\); Table 2).

**Blood glucose levels**

The blood glucose level in group X after treatment was notably lower compared with group Y (\(p < 0.001\); Table 3).

<p>| Table 1: Comparison of treatment effectiveness [n (%), n = 93] |
|------------------|------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Markedly effective</th>
<th>Effective</th>
<th>Ineffective</th>
<th>Total effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>53(56.99)</td>
<td>38(40.86)</td>
<td>2(2.15)</td>
<td>91(97.85)</td>
</tr>
<tr>
<td>Y</td>
<td>43(46.24)</td>
<td>38(40.86)</td>
<td>12(12.90)</td>
<td>81(87.1)</td>
</tr>
<tr>
<td>(\chi^2)</td>
<td>2.153</td>
<td>0.000</td>
<td>7.724</td>
<td>7.724</td>
</tr>
<tr>
<td>(P)-value</td>
<td>0.142</td>
<td>1.000</td>
<td>0.005</td>
<td>0.005</td>
</tr>
</tbody>
</table>

<p>| Table 2: Comparison of incidence of adverse reactions [n(%)] |
|-----------------|------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Group</th>
<th>Nausea and vomiting</th>
<th>Diarrhea</th>
<th>Headache</th>
<th>Hypoglycemia</th>
<th>No adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>1(1.08)</td>
<td>0(0.00)</td>
<td>0(0.00)</td>
<td>1(1.08)</td>
<td>91(97.85)</td>
</tr>
<tr>
<td>Y</td>
<td>4(4.30)</td>
<td>2(2.15)</td>
<td>3(3.23)</td>
<td>5(5.38)</td>
<td>79(84.95)</td>
</tr>
<tr>
<td>(\chi^2)</td>
<td>1.850</td>
<td>2.022</td>
<td>3.049</td>
<td>2.756</td>
<td>12.109</td>
</tr>
<tr>
<td>(P)-value</td>
<td>0.174</td>
<td>0.155</td>
<td>0.081</td>
<td>0.097</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Table 3: Comparison of blood glucose levels (mean ± SD, mmol/L)

<table>
<thead>
<tr>
<th>Group</th>
<th>FBG</th>
<th>2 h PBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>5.67 ± 1.02</td>
<td>7.01 ± 1.03</td>
</tr>
<tr>
<td>Y</td>
<td>6.98 ± 1.37</td>
<td>8.68 ± 1.55</td>
</tr>
<tr>
<td>T</td>
<td>7.396</td>
<td>8.654</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Note: FBG = fasting blood glucose level; PBG = 2-hour postprandial blood glucose level

**TCM syndrome scores**

The TCM syndrome score in group X (2.61 ± 0.27) after treatment was significantly lower than in group Y (5.22 ± 1.08, p < 0.001).

**Serum C-peptide levels**

The post-treatment serum C-peptide level was significantly up-regulated in group X, relative to group Y (p < 0.001; Figure 1).

**HbAlc levels before and after treatment**

Group X had markedly lower HbAlc level than group Y (p < 0.001; Figure 2).

**DISCUSSION**

The number of DM cases worldwide has exceeded 400 million, of which Chinese DM patients account for 25%, and spend more than one trillion annually on the treatment, indicating that the disease has become a serious social and medical problem [16]. Patients with DM are prone to cardiovascular diseases, kidney diseases and other organ diseases due to changes in blood glucose which seriously affect the physical and mental status of patients. In addition, continuous medication after diagnosis leads to gradually decreasing compliance and uncontrolled complications in patients. Therefore, early intervention in diagnosis and treatment can effectively alleviate the condition and reduce the possibility of complications.

Serum C peptide and HbAlc are clinical indicators used for the diagnosis and treatment of DM. Indeed, HbAlc is known as the gold standard for evaluating the efficacy of DM due to an irreversible reaction between HbAlc and blood glucose, and lower HbAlc indicates better DM control [17]. This study showed improved HbAlc levels in both groups, because metformin directly acts on glucose metabolism, accelerates the decomposition of glucose, and enhances the absorption capacity of peripheral tissues while reducing glucose absorption and inhibiting hepatic glucose production. There was lower post-treatment HbAlc level in group X than in group Y, due to the efficacy of Gegen Cenlian decoction. Gegen Cenlian decoction contains many Chinese herbs such as *Salvia miltiorrhiza* and *Scutellaria baicalensis*. *Salvia miltiorrhiza* relieves pain, while *Scutellaria baicalensis* removes toxins and expels pus, and there is a good synergistic effect between the two drugs. In addition, *radix Rehmanniae recens* nourishes *yin* and blood, and *Pueraria montana var. lobata* relieves symptoms and removes heat. The combination of multiple drugs has substantial benefits in the treatment of DM. Thus, group X showed better blood biochemical indices and blood glucose control than group Y.

Although metformin controls blood glucose level, it has limited application due to its short-term effect in patients during medication, and adverse reaction such as diarrhea. Gegen Cenlian decoction improved the patients' physical conditions, promoted blood circulation and removed blood stasis. Moreover, Chinese medicinal materials do not cause toxic and side effects, and do not cause serious drug reactions. Therefore, group X had a lower TCM syndrome...
score and a lower possibility of adverse reactions in patients.

There was higher treatment effectiveness in group X than in group Y. In a study by Horii et al., DM patients in experimental group received metformin in combination with Chinese medicinal herbs such as Scutellaria baicalensis and Salvia miltiorrhiza, while those in the control group received metformin only. There was markedly higher treatment effectiveness in the experimental group (98.00%) than in control group [18]. This is in agreement with the results obtained in the present research, and it reveals that the medicinal materials in Gegen Cenlian decoction effectively enhanced therapeutic effect of metformin on DM patients and achieved the therapeutic goal.

CONCLUSION

Gegen Qinlian decoction in combination with metformin demonstrates higher efficacy in DM patients than metformin alone. The combined therapy also produces a low incidence of adverse reactions in patients. Therefore, the combined therapy has potentials for use in clinical practice, but further clinical trials are required application.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Jie Chen and Weijuan Li conceived and designed the study, and drafted the manuscript. Jie Chen, Yi Xu, Yan Zhao, Geling Liu, Jia Cui and Yan Li collected, analyzed and interpreted the experimental data. Yi Xu and Weijuan Li revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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