Effect of adjuvant salvia miltiorrhiza and ligustrazine therapy on renal function, renal blood perfusion as well as CTGF and TGF-\(\beta\) 1 content in patients with chronic renal failure

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ARTICLE INFO

Objective: To analyze the effect of adjuvant salvia miltiorrhiza and ligustrazine therapy on renal function, renal blood perfusion as well as connective tissue growth factor (CTGF) and transforming growth factor (TGF)-\(\beta\) 1 content in patients with chronic renal failure. Methods: 80 patients with chronic renal insufficiency treated in our hospital between March 2013 and March 2016 were selected for study and randomly divided into observation group (n=40) and control group (n=40). Control group received conventional therapy and observation group received conventional + adjuvant salvia miltiorrhiza and ligustrazine therapy. After 3 months of treatment, differences in renal function indexes, illness-related indexes, renal blood perfusion, CTGF and TGF-\(\beta\) 1 content, and so on of two groups of patients were determined. Results: After 3 months of treatment, serum urea nitrogen (BUN), serum creatinine (Scr), \(\beta\) 2 microglobulin (\(\beta\) 2-MG), intermedin (IMD), fibroblast growth factor 23 (FGF23), cystatin C (CysC), CTGF and TGF-\(\beta\) 1 content as well as 24 h urine albumin excretion rate (UAER) level in urine of observation group were significantly lower than those of control group (\(P<0.05\)) while glomerular filtration rate (GFR) level and serum adiponectin (APN) content were significantly higher than those of control group (\(P<0.05\)); renal perfusion parameters renal cortex Tmax (ATc) and medulla Tmax (ATm) levels of observation group were significantly lower than those of control group while cortex peak intensity change (\(\Delta\)Ac), medulla peak intensity change (\(\Delta\)Am) and peak intensity (PI) levels were significantly higher than those of control group. Conclusions: Adjuvant salvia miltiorrhiza and ligustrazine therapy can effectively control the overall condition of patients with chronic renal failure, and plays a positive role in improving renal function and increasing renal blood perfusion.

1. Introduction

Since the onset, the renal function of patients with chronic renal failure will continue to deteriorate and end up with uremia, and how to delay the process of renal function deterioration is the hot topic of clinical research at present. Patients with chronic renal failure are accompanied with proteinuria, electrolyte and acid-base balance disorders, low-protein diet, adjusting water-electrolyte disturbance, correcting acidosis, controlling hypertension and so on are the conventional symptomatic treatments, they can reduce the illness severity to a certain extent, but their roles in inhibiting the disease progress is still limited[1]. The traditional Chinese medicine is with long time of study on chronic renal failure, and holds that the main causes of disease are glomerular fibrosis-induced kidney atrophy, loss of normal metabolism, etc[2]. Salvia miltiorrhiza and ligustrazine is highly recognized by traditional Chinese medicine and can optimize the renal function, the drug was used as an auxiliary therapy in the study and added in the treatment of patients with chronic renal insufficiency in our hospital, and the effect of adjuvant salvia miltiorrhiza and ligustrazine therapy on renal function, renal blood perfusion as well as CTGF and TGF-\(\beta\) 1 content in patients with chronic renal failure was mainly analyzed.

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\[\text{Fund project: Science and Technology Planning Project of Guangdong Province (No: 2012B031600471).}\]
2. Materials and methods

2.1. General information

80 patients with chronic renal insufficiency treated in our hospital between March 2013 and March 2016 were selected, inclusion criteria: (1) in accordance with the diagnostic criteria for chronic renal failure; (2) diagnosed and systemically treated for the first time; (3) understood the research process and signed the informed consent. Exclusion criteria: (1) with primary or metastatic renal malignant tumor; (2) with severe heart and liver insufficiency; (3) associated with autoimmune diseases; (4) with acute systemic infectious disease; (5) pregnant or breastfeeding women. Random number table was used to divide the included patients into observation group and control group, 40 cases in each group. Control group included 19 male cases and 21 female cases that were 33–70 years old, and with the course of renal insufficiency 1–7 years and (3.09±0.67) years in average; observation group included 22 male cases and 18 female cases that were 35–72 years old, and with the course of renal insufficiency 1–8 years and (3.42±0.76) years in average. The two groups of patients were not statistically different in the distribution of gender, age and course of disease \((P>0.05)\) and they were comparable.

2.2. Treatment methods

Control group of patients received clinical conventional therapy for chronic renal insufficiency, which was specific as follows: low-protein and low-calcium diet, adjusting water-electrolyte disturbance, correcting acidosis, controlling hypertension, etc. Observation group received conventional + auxiliary salvia miltiorrhiza and ligustrazine therapy, specifically as follows: 15 mL salvia miltiorrhiza + ligustrazine injection in 300 mL 5% glucose injection, slow intravenous drip, 1 time a day for 3 consecutive months. Conventional therapy was the same as that of control group.

2.3. Renal function evaluation methods

After 3 months of treatment, 2 mL of fasting peripheral venous blood was collected from the patients, let stand at room temperature and then centrifuged at high speed to get supernatant, automatic biochemical analyzer was used to determine blood urea nitrogen (BUN), serum creatinine (Scr) and \(\beta\)-2 microglobulin (\(\beta\)-2-MG) content, glomerular filtration rate (GFR) was calculated; enzyme-linked immunosorbent assay kits were used to determine intermedin (IMD), fibroblast growth factor 23 (FGF23), cystatin C (CysC) and adiponectin (APN) content as well as connective tissue growth factor (CTGF) and transforming growth factor (TGF)-\(\beta\) 1 content. Urine samples were collected from patients to determine 24 h urine albumin excretion rate (UAER).

2.4. Renal blood perfusion

After 3 months of treatment, Philips diasonograph was used to test renal perfusion, abdominal convex array probe and pulse-reverse harmonics technique were selected, and the specific perfusion parameters included renal cortex Tmax (ATc), cortex peak intensity change (ΔAc), medulla Tmax (ATm), medulla peak intensity change (ΔAm) and peak intensity (PI).

2.5. Statistical analysis

SPSS23.0 software was used to input data, measurement data analysis between two groups was by \(t\) test and \(P<0.05\) indicated statistical significance in differences.

3. Results

3.1. Renal function indexes

After 3 months of treatment, comparison of renal function indexes BUN, Scr, \(\beta\)-2-MG, GFR and UAER between two groups of patients is as follows: serum BUN, Scr and \(\beta\)-2-MG content as well as UAER level in urine of observation group were significantly lower than those of control group \((P<0.05)\) while GFR level was significantly higher than that of control group \((P<0.05)\) (Table 1).

<table>
<thead>
<tr>
<th>Groups</th>
<th>BUN (mmol/L)</th>
<th>Scr (μmol/L)</th>
<th>(\beta)-2-MG (mg/L)</th>
<th>GFR (mL/min)</th>
<th>UAER (mg/24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>6.18±0.73</td>
<td>94.37±9.12</td>
<td>0.21±0.03</td>
<td>76.52±8.73</td>
<td>82.76±8.15</td>
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<tr>
<td>Control group</td>
<td>9.22±0.95</td>
<td>117.52±14.83</td>
<td>0.32±0.37</td>
<td>64.69±7.15</td>
<td>115.42±14.53</td>
</tr>
<tr>
<td>(t)</td>
<td>7.932</td>
<td>12.183</td>
<td>5.192</td>
<td>7.943</td>
<td>9.782</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

3.2. Illness-related indexes

After 3 months of treatment, comparison of serum illness-related indexes IMD, FGF23, CysC and APN between two groups of patients is as follows: serum IMD, FGF23 and CysC content as well as APN level in urine of observation group were significantly lower than those of control group \((P<0.05)\) while GFR level was significantly higher than that of control group \((P<0.05)\) (Table 2).

<table>
<thead>
<tr>
<th>Groups</th>
<th>BUN (mmol/L)</th>
<th>Scr (μmol/L)</th>
<th>(\beta)-2-MG (mg/L)</th>
<th>IMD (pg/mL)</th>
<th>CysC (mg/L)</th>
<th>FGF23 (pM/L)</th>
<th>APN (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>6.18±0.73</td>
<td>94.37±9.12</td>
<td>0.21±0.03</td>
<td>152.3±14.83</td>
<td>1.43±0.37</td>
<td>18.2±14.83</td>
<td>1.23±0.37</td>
</tr>
<tr>
<td>Control group</td>
<td>9.22±0.95</td>
<td>117.52±14.83</td>
<td>0.32±0.37</td>
<td>178.2±14.83</td>
<td>2.67±0.78</td>
<td>21.3±14.83</td>
<td>1.85±0.57</td>
</tr>
<tr>
<td>(t)</td>
<td>7.932</td>
<td>12.183</td>
<td>5.192</td>
<td>2.52±0.78</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Table 1
Comparison of renal function indexes between two groups of patients after treatment \((n=40, \bar{X}±s)\).
Comparison of renal blood perfusion parameters between two groups of patients after treatment ($n=40$, $\pm s$).

<table>
<thead>
<tr>
<th>Groups</th>
<th>ATc (s)</th>
<th>ΔAc</th>
<th>ATm (s)</th>
<th>ΔAm</th>
<th>PI (dB)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group</td>
<td>5.73±0.61</td>
<td>91.37±6.98</td>
<td>6.49±0.72</td>
<td>70.37±8.12</td>
<td>22.61±2.85</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Control group</td>
<td>7.19±0.84</td>
<td>67.39±7.12</td>
<td>10.17±1.96</td>
<td>58.49±6.12</td>
<td>8.364</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$t$</td>
<td>5.934</td>
<td>9.723</td>
<td>8.201</td>
<td>9.173</td>
<td>8.364</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>$P$</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

3.3. Renal blood perfusion

After 3 months of treatment, comparison of renal blood perfusion parameters ATc, ΔAc, ATm, ΔAm and PI between two groups of patients is as follows: ATc and ATm levels of observation group were significantly lower than those of control group ($P<0.05$) while ΔAc, ΔAm and PI levels were significantly higher than those of control group ($P<0.05$) (Table 3).

3.4. CTGF and TGF-β 1 content

After 3 months of treatment, comparison of serum CTGF and TGF-β 1 content between two groups of patients is as follows: serum CTGF content of observation group was (23.84±4.07) μg/L and TGF-β 1 content was (14.76±2.18) μg/L after treatment while serum CTGF content of control group was (35.91±4.14) μg/L and TGF-β 1 content was (23.92±2.53) μg/L after treatment. Serum CTGF and TGF-β 1 content of observation group were significantly lower than those of control group ($P<0.05$).

4. Discussion

Symptomatic treatment of western medicine can reduce the severity of chronic renal failure to a certain extent, but its role in reversing renal function and delaying the disease progression has been questioned by the majority of scholars. How to effectively optimize the therapeutic effect of chronic renal failure is a hot spot in current research, and the addition of Chinese patent medicine is expected to break the current bottleneck. The main ingredients of salvia miltiorrhiza and ligustrazine are salvia miltiorrhiza and ligustrazine, salvia miltiorrhiza can remove stasis to ease pain and activate blood to promote menstruation and ligustrazine can control inflammation, regulate immune function, and so on. The drug has already been successfully applied in the treatment of acute glomerulonephritis, but it is less reported in the treatment of chronic renal failure, salvia miltiorrhiza and ligustrazine was used as adjuvant therapy in the study, added in the treatment of patients with chronic renal failure in our hospital, and mainly studied from renal function, renal perfusion and other aspects.

Renal dysfunction is the most intuitive and the main feature in patients with chronic renal failure, and with the aggravation of disease, the levels of typical indexes such as BUN, Scr, β 2-MG, GFR and UAER fluctuate significantly[3,4]. Numerous studies have demonstrated that the GFR decline is the first performance of renal failure, and with continuous GFR decline, the adverse metabolites in the body cannot be discharged, and BUN, Scr and β 2-MG massively accumulate in the body. In the study, renal function indexes of both groups were tested at first at the same point in time after 3 months of treatment, and it was found that BUN, Scr and β 2-MG content as well as UAER level of observation group were lower ($P<0.05$) while GFR level was higher ($P<0.05$), showing that adjuvant salvia miltiorrhiza and ligustrazine therapy helps to improve the glomerular filtration rate and discharge the metabolites in patients with chronic renal failure, and the homeostasis is greatly recovered. In addition to basic renal function indexes, there are many factors in serum that are directly related to the kidney damage, and detecting their contents can indirectly reflect the clinical therapeutic effect. IMD, FGF23, CysC and APN are the effective indicators to judge the early renal damage, single detection sensitivity and specificity are not high, but the joint detection has strong directivity to renal damage[5,6]. Study has shown that after trace IMD injection, sober rats can show renal vasodilation and drop of blood pressure, it is a reactive factor for hypertension, and as hypertension levels increase, IMD secretion increases. FGF23 is expressed in osteoblasts and then reaches the kidney with the blood circulation, it can maintain the normal calcium phosphate levels in the body, and FGF23 generation increases under the stimulation of hypercalcemia. Kidney is the only organ to clear CysC, and CysC content may increase in the early stage of renal function decline[7]. APN has multiple roles such as anti-inflammation, anti-platelet aggregation and anti-atherosclerosis, and its content decrease is one of the important causes of sustained progress of renal failure[8]. The study results showed that the serum IMD, FGF23 and CysC content of observation group were lower ($P<0.05$) while APN content was higher after treatment ($P<0.05$), confirming that the renal function optimization of the group was better after treatment, and further illustrating the outstanding effect of the adjuvant salvia miltiorrhiza and ligustrazine therapy on optimizing renal function.

The realization of renal functions depends on the maintenance of...
normal blood supply, and one of the important mechanisms of the renal failure is the reduced renal perfusion[9]. Studies show that renal blood flow perfusion is positively correlated with glomerular filtration rate, so two groups of patients received ultrasonic renal perfusion detection after treatment in the study, and it was found that the ATc and ATm of observation group were shorter while ΔAc, ΔAm and PI were bigger (P<0.05). Many studies have pointed out that there are ATc and ATm extension in patients with abnormal renal function, which is associated with the reduced renal cortex and medulla perfusion and the decreased infusion speed[10]. Patients with chronic renal failure are mostly with microvessel embolism and small vessel spasm, leading to the decrease in the number of renal parenchyma microbubble and the reduction in backscatter intensity[11]. The above results show that salvia miltiorrhiza and ligustrazine can dredge renal blood vessels and increase renal perfusion.

New studies have found that renal fibrosis is the important cause of declining kidney function, CTGF and TGF-β 1 are fibrosis indexes, and their content changes in patients with chronic renal failure have been widely concerned[12,13]. TGF-β 1 is the main factor that leads to renal interstitial fibrosis, and it can prompt renal extracellular matrix accumulation, up-regulate collagen mRNA expression and increase collagen synthesis. CTGF is TGF-β 1 downstream signal factor, which is massively generated when induced by TGF-β 1, and the current researches have confirmed that a high level of CTGF is closely related to the occurrence of IgA nephropathy, lupus nephritis and mesangial proliferative nephros[14-16]. In the study, serum CTGF and TGF-β 1 content of observation group were lower after 3 months of treatment (P<0.05), indicating that salvia miltiorrhiza and ligustrazine can also inhibit renal fibrosis, and showing that the realization of renal function improvement effect of salvia miltiorrhiza and ligustrazine is related to its anti-fibrosis function.

To sum up, it is concluded as follows: adjuvant salvia miltiorrhiza and ligustrazine therapy can effectively control the overall condition of patients with chronic renal failure, plays a positive role in improving renal function and increasing renal blood perfusion, and is worth popularization and application in clinical practice in the future.

References