EFFECT OF COMBINATION OF YANYU TONGLUO PLASTER AND CELECOXIB CAPSULE ON TREATMENT OF KNEE OSTEOARTHRITIS

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ABSTRACT

Objective: To investigate the effect of combination of Yanyu tongluo plaster and celecoxib capsule on treating knee osteoarthritis, and its impact on serum and knee joint fluid levels of irisin and SDF-1.

Methods: Knee osteoarthritis patients (numbering 400) admitted to the Department of Orthopaedics and Traumatology, Affiliated Hospital of Nanjing University from January 2013 to January 2016 were recruited into the study. They were randomly assigned to either control group or observation group (200/group). All patients received celecoxib, but those in the observation group were given Yanyu tongluo plaster. Treatment effectiveness, improvement of specific clinical manifestations, and levels of knee joint fluid SDF-1 and serum irisin were assayed in the two groups using enzyme-linked immunosorbent assay (ELISA).

Results: Total clinical effectiveness in the observation group (91.5%) was much higher than that of the control group (75.5%, p < 0.05). There were no significant differences in Lysholm scores and VAS scores between the two groups before treatment (p > 0.05). However, after treatment, the Lysholm scores of two groups increased significantly, but values in the observation group were significantly higher than corresponding values in the control group (p < 0.05). Moreover, the VAS scores of two groups decreased significantly, but VAS scores in the observation group was much less than VAS scores in the control group (p < 0.05). No significant differences existed serum SDF-1 and irisin or knee joint fluid between the two groups before treatment. After treatment, serum SDF-1 and knee joint fluid in the two groups decreased significantly, but these parameters were significantly lower in the observation group than in the control group (p < 0.05). Similarly, serum irisin and knee joint fluid of two groups were significantly increased after treatment, but their levels in the observation group were much higher than those in the control group (p < 0.05).

Conclusion: The combination of Yanyu tongluo plaster and celecoxib may play a positive role in treating knee osteoarthritis through regulation of serum SDF-1 and irisin or knee joint fluid. This finding merits further exploration with a view to adopting them for clinical application.

Keywords: Yanyu tongluo plaster, Celecoxib capsule, Knee osteoarthritis, SDF-1, Irisin.

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Introduction

Knee osteoarthritis is the main cause of knee pain in the aged. A survey has shown that the incidence of knee osteoarthritis in men and women are 24.7% and 54.6%, respectively, and it increases with age, resulting in a heavy social burden(1). Presently, there are no specific and effective orthodox methods for treating knee osteoarthritis. However, it is claimed that plasters from traditional Chinese medicine (TCM) have unique advantages in the treatment of the disease. In this study, the clinical effect of Yanyu tongluo plaster on knee osteoarthritis and its potential mechanism were investigated.

Clinical data and methods

General data on subjects: Outpatients (400) with knee osteoarthritis admitted to the Department of Orthopedics and Traumatology, Affiliated Hospital of Nanjing University from January 2013 to January 2016 were enrolled in the study. They were randomly assigned into control group and observa-
tion group (200 patients/group). All of them met the inclusion criteria. In the control group, there were 99 males and 101 females aged from 43 to 78 years (mean age = 65.37 ± 5.42 years), with disease durations from 2 months to 6 years (mean duration = 3.22 ± 1.43 years). There were 56 cases of left knee pain, 59 cases of right knee pain, while 85 patients had pain in both knees. In the observation group, there were 98 males and 102 females aged from 41 to 77 years (mean age = 66.89 ± 6.37 years), with disease duration ranging from 1 month to 6.5 years (mean duration = 4.01 ± 1.74 years). There were 60 cases of left knee pain, 58 cases of right knee pain, and 82 cases of pain in both knees. There were no differences in age, sex, time of onset, and physical activities engaged in between the two groups (p > 0.05). All patients signed informed consent forms.

**Methods**

- **General treatment:** The patients were guided to do active but non-strenuous movement to strengthen the quadriceps-based muscle.
- **Medications:** Both groups were given celecoxib capsules (Pfizer Pharmaceutical Co., Ltd., 200mg, twice a day, 6 weeks for a course of treatment, 3 courses in total. In addition, the observation group received treatment with Yanyu tongluo plaster (Quzhou Nankong Chinese Medicine Co., Ltd). The ingredients of Yanyu tongluo plaster were 2250 g of Yujin (Radix curcumae) and 4500 g of Yanhusuo (Rhizoma corydalis). These two were dried and ground. The powder was sieved and stirred with white vinegar into a mush at room temperature, and put into a ceramic bottle for 3 days. To make the plaster, 30 g of the drug mush was evenly prepared as a circular paste with diameter of 7.5 cm and the thickness of 0.2 cm, and the plaster was applied on the affected knee with appropriate fixation, once every two days, one month for a treatment course, 3 courses in total. During the treatment, the doctors paid attention to the patients’ conditions such as red or itching skin.

**Sample collection and analysis**

Venous blood (5 ml) was taken from each patient before and after treatment, and centrifuged to get serum which refrigerated at -70°C. Knee joint fluid (3-5 ml) was taken with a 5 ml syringe under aseptic condition before and after treatment, centrifuged to get supernatant fluid which was stored in a refrigerator at -70°C. Reagent kits for SDF-1 and irisin were separately used to determine the levels of SDF-1 and irisin in serum and knee joint fluid by ELISA.

**Observation indices:**

The clinical efficacy of treatments in the two groups were determined based on the following classification and criteria:\[markedly effective\]: great improvement in patients’ knee pain and swelling, and knee functions getting back to normal so that they can perform normal physical activities; \[effective\]: patients’ knee pain and swelling getting better, with partial recovery of knee function, so they can move without help and conduct some physical activities they could not do before treatment; \[ineffective\]: no relief from the patients’ knee pain and swelling, with even worse knee function.

**Diagnostic criteria**

Western medicine (WM) diagnostic criteria: All patients were diagnosed in line with the diagnostic criteria of Guideline on Diagnosis and Treatment of Osteoarthritis\(^2\). The criteria are knee pain within the last one month; friction in knee joints when walking, accompanied by morning stiffness lasting less than 30 minutes; changes in X-images, such as narrowing of the knee joint and bone spur formation; cool and thick joint fluid, and white blood cells < 2000 / mL.

**TCM diagnostic criteria:** All patients were also diagnosed in accordance with TCM Syndrome Diagnosis and Efficacy Criteria\(^3\). The criteria include knee pain and heaviness, inflexible joints, swollen joint; paleness and pyrexia, aggravated by cold but improved by heat; pale tongue with white, greasy or slippery coating, and wiry and tense pulse.

**Inclusion and exclusion criteria**

Patients who met the following criteria were included: diagnosis of knee osteoarthritis with the diagnostic criteria of WM and TCM for knee osteoarthritis, and patients in normal mental condition with consciousness and good compliance. Patients with tumors of skeletal system, bone metastasis due to other cancers, and dysfunction of vital organs like liver and kidney, were excluded. In addition, patients with mental disorder, rheumatoid or autoimmune arthritis, and patients with recent medication recently, as well as those who were allergic to the drugs used in the study, and patients who did not sign informed consent forms, were all excluded.
Total effectiveness = (markedly effective cases + effective cases) / the total subjects ×100%

Assessment of the clinical symptoms of patients
Knee function was evaluated using the Lysholm scale. In this scale, the higher the score, the better the knee function. Degree of knee pain was assessed using Visual Analogue Scale (VAS). The patients chose corresponding numbers based on their own feeling on a note marked with numbers from 0 to 10. The larger the number is, the more intense the pain. The level of SDF-1 and irisin in serum or knee joint fluid of two groups.

Statistic analysis
All data were analyzed with software SPSS19.0. The normal distribution measurement data were expressed as mean ± standard deviation (χ±s), and t-test was used for the comparison between groups. Enumeration data were expressed as ratios, and Chi square (χ²) test was used for comparison between groups. Values of p < 0.05 were taken as indicative of statistically significant differences.

Results

Assessment of the clinical effectiveness of treatments in the two groups
The total clinical effectiveness in the observation group was 91.35%, while that of the control group was 75.5% (p < 0.05, Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>Markedly effective cases</th>
<th>Effective cases</th>
<th>Ineffective cases</th>
<th>Total effectiveness (%)</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>64</td>
<td>87</td>
<td>49</td>
<td>75.5</td>
<td>18.58</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Observation</td>
<td>101</td>
<td>82</td>
<td>17</td>
<td>91.55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Clinical effectiveness of treatments in the two groups.

Assessment of clinical symptoms in the two groups
There were no significant differences in Lysholm scores between the two groups before treatment (p > 0.05). However, after treatment, the Lysholm scores of two groups increased significantly, but were higher in the observation group than in the control group (p < 0.05, Table 2).

Comparison of the VAS scores of two groups before treatment showed no difference (p > 0.05). However, after treatment, the VAS scores of two groups were significantly decreased, although the

<table>
<thead>
<tr>
<th>Group</th>
<th>Before treatment</th>
<th>One month after treatment</th>
<th>Three months after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>55.37±6.33</td>
<td>70.28±3.97</td>
<td>80.89±8.01</td>
</tr>
<tr>
<td>Observation</td>
<td>56.0±4.68</td>
<td>81.85±7.74</td>
<td>88.16±7.24</td>
</tr>
</tbody>
</table>

Table 2: Comparison of Lysholm scores of the two groups (χ²).

Comparison of the VAS scores of the two groups (χ²).

<table>
<thead>
<tr>
<th>Group</th>
<th>Before treatment</th>
<th>One month after treatment</th>
<th>Three months after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.08±1.22</td>
<td>6.63±2.05</td>
<td>5.26±3.08b</td>
</tr>
<tr>
<td>Observation</td>
<td>7.17±1.35</td>
<td>5.20±1.93ce</td>
<td>4.19±1.61df</td>
</tr>
</tbody>
</table>

Table 3: Comparison of the VAS scores of the two groups (χ²).

Levels of SDF-1 and irisin in serum or knee joint fluid of two groups
Comparison of the two groups showed no significant difference in the serum level of SDF-1 or knee joint fluid before treatment (p > 0.05). However, after treatment, the serum levels of SDF-1 or knee joint fluid of two groups decreased significantly (p < 0.05), but SDF-1 level of the observation group was (p < 0.05, Table 4).

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum SDF-1 (ug/L)</th>
<th>Knee joint fluid SDF-1 (ug/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Control</td>
<td>10.92±2.03</td>
<td>7.85±1.17d</td>
</tr>
<tr>
<td>Observation</td>
<td>11.03±2.99</td>
<td>5.62±0.87d</td>
</tr>
</tbody>
</table>

Table 4: Comparison of the level of SDF-1 in serum or knee joint fluid of the two groups.

Effect of combination of Yanyu Tongluo plaster and celecoxib capsule on treatment of knee osteoarthritis
ment (p > 0.05). After the treatment, the level of irisin in serum or knee joint fluid of two groups increased significantly, but the observation group had much higher irisin levels than the control group (p < 0.05, Table 5).

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum irisin (ug/L)</th>
<th>Knee joint fluid irisin (ug/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Control</td>
<td>315.46±28.74</td>
<td>487.56±33.15</td>
</tr>
<tr>
<td>Observation</td>
<td>317.0±30.86</td>
<td>569.35±39.95</td>
</tr>
</tbody>
</table>

Table 5: Comparison of the irisin level in the serum or knee joint fluid of the two groups (χ²).

Discussion

At the early stage of osteoarthritis, the symptoms are mild but become gradually aggravated if there are no timely and proper treatments. Its main clinical manifestations include knee joint aching, swelling, stiffness, deformity, and difficulties in walking. Some patients may even lose the ability to walk, thereby affecting their mental health and quality of life. The pathogenesis of osteoarthritis is unknown at present, but it may be associated with several factors such as knee joint degeneration, overweight, improper walking posture, and excess strain. Presently, there is no specific method for the treatment of knee osteoarthritis. In clinics, the main treatment principle is to protect knee joints, improve symptoms, and promote the repair of cartilago articularis so as to relieve the clinical manifestations or even cure it.

Traditional Chinese medicine (TCM) has profound understanding of knee osteoarthritis. It is believed in TCM that this disease belongs to the category of Bi syndrome and Knee Bi caused by liver-kidney deficiency, and congestion, sputum and phlegm due to the invasion of pathogenic wind, cold, and wetness.

Celecoxib capsule is a drug for the treatment of knee osteoarthritis. However, it has various side effects on the digestive system, immune system, reproductive system, circulatory system, respiratory system, and skin. Thus, its clinical efficacy and application are limited. The plaster of Chinese medicine refers to a therapy that applies drugs on knee joints, with appreciable safety and effect.

In this study, Yanyu tongluo plaster was used to treat knee osteoarthritis, and it resulted in significant curative effects. Clinical manifestations and knee joint function in the observation group were much more improved, and the total effectiveness was much higher than that of the patients who took celecoxib. This finding is in line with previous reports on treatment of knee osteoarthritis using Chinese medicine.

In order to investigate the mechanisms of action of Yanyu tongluo plaster, levels of SDF-1 and irisin in serum and knee joint fluid of the patients were assessed. The levels of SDF-1 in patients’ serum and knee joint fluid were reduced significantly, but irisin levels rose appreciably after Yanluo tongluo plaster treatment. Stromal-derived factor -1 (SDF-1) belongs to the family of chemokine proteins. Studies have shown that SDF-1 can activate the signal pathways on the surface of articular cartilage cells and induce the degradation of cartilage matrix. Moreover, addition of DF-1 to the cartilage cell culture solution can induce degradation of cartilage matrix. This suggests that SDF-1 may aggravate the condition of patients with knee osteoarthritis. Irisin is closely related to skeletal metabolism. The findings of an animal experiment revealed that exercise enhanced the secretion of irisin and promoted the differentiation of osteocytes, and that irisin levels are positively linked to differentiation of osteocytes. It can be inferred that irisin may promote the differentiation and maturation of osteocytes and thus participate in the healing of knee osteoarthritis.

In essence, this study has demonstrated that combination of Yanyu tongluo plaster and celecoxib was able to treat knee osteoarthritis with good effectiveness, most likely due to regulation of SDF-1 and irisin levels.

References


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