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Retrospective Study

Potential role of the compound Eucommia bone tonic granules in patients with osteoarthritis and osteonecrosis: A retrospective study

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Abstract

BACKGROUND

Osteoarthritis is a major source of pain, disability, and socioeconomic cost worldwide. Osteonecrosis is a disabling disorder that frequently occurs in the younger population aged from 20-50 years. The compound Eucommia bone tonic granules, a traditional Chinese medicine, can alleviate the damage of osteoarthritis and osteonecrosis.

AIM

To investigate the potential role of the compound Eucommia bone tonic granules (Eucommia) in the treatment of patients with osteoarthritis and osteonecrosis.

METHODS

One-hundred forty osteoarthritis and osteonecrosis cases admitted to our hospital from January 2013 to December 2017 were selected. Patients were divided into two groups: Eucommia-meloxicam group and meloxicam group. Clinical efficacy and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score were evaluated according to the evaluation criteria of orthopedic diseases. The levels of bone-GLA protein, interleukin-17, recombinant human S100 calcium binding protein A12, sphingosine 1-phosphate, cystatin C, creatinine, and hemoglobin in peripheral blood were determined.

RESULTS

The total effective rate in the two osteoarthritis groups was not different, but the total effective rate in the two osteonecrosis groups was significantly different. The overall efficacy of Eucommia-meloxicam group was superior to that of the meloxicam group. WOMAC showed that pain, stiffness, and dysfunction in the two groups of osteoarthritis and osteonecrosis before and after treatment were

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significantly different. The concentration of recombinant human S100 calcium binding protein A12, sphingosine 1-phosphate, cystatin C, creatinine, and hemoglobin before and after treatment in the Eucommia-meloxicam group and meloxicam group of osteoarthritis and osteonecrosis were significantly different, and the two treatment groups were significantly different from each other for osteoarthritis.

CONCLUSION

Our findings indicate that Eucommia can effectively enhance the curative effect of meloxicam, and the combination of Eucommia and meloxicam is superior to meloxicam alone.

Key words: Osteoarthritis; Osteonecrosis; Eucommia; Patients; Meloxicam; Drug

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Core tip: Eucommia enhances the curative effect of meloxicam, and combining Eucommia and meloxicam is effective for the treatment of osteoarthritis and osteonecrosis.

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INTRODUCTION

Osteoarthritis is a chronic degenerative disease of articular cartilage. Due to the special pathological location of bone joints, osteoarthritis can be diagnosed through imaging and relevant biochemical indicators^[1-3]. The main pathological changes of osteoarthritis are cartilage matrix degradation, osteophyte hyperplasia, and osteophyte formation around cartilage^[4]. Osteonecrosis is a disease caused by multiple factors that disrupt the blood supply of the femoral head, leading to the death of bone cells or the destruction of surrounding tissues, and finally causing joint surface collapse and osteoarthritis^[5]. The traditional Chinese medicine *Eucommia ulmoides* Oliver (Eucommiaceae) can strengthen the spleen and tonify the kidney, stop stasis, and decrease turbidity.

Eucommia contains a variety of bioactive chemicals, including lignans, iridoids, phenolics, steroids, terpenoids, flavonoids, *etc.* These bioactive chemicals function effectively to nourish the liver and kidneys and regulate blood pressure and have been used to treat bone fractures and other bone diseases. The composition of bioactive chemicals extracted from Eucommia varies depending on the functional part (leaves, seeds, bark, and staminate flower) and planting models. The bioactive parts of Eucommia are widely used as raw materials for medicine and food, powdery extracts, herbal formulations, and tinctures. These capabilities hold potential for future development and commercial exploitation of the bioactive products from Eucommia^[6].

The stem bark of Eucommiaceae, which is also known as Du-Zhong, is commonly utilized in traditional Chinese medicine for the treatment of rheumatoid arthritis^[7]. Eucommia is the main component of the compound Du-Zhong bone tonic granules. Modern pharmacological and molecular biology studies have supported these traditional uses and suggest that crude extracts and total glycosides of *Eucommia ulmoides* may yield safe and mild anti-osteoporosis agents^[8]. Eucommia may inhibit the progression of osteoarthritis by inhibiting the phosphoinositol 3-kinase/Akt pathway to delay cartilage degeneration, reduce inflammatory cytokines, and prevent matrix metalloproteinase-3 secretion^[9]. Eucommia has a cartilage-protecting effect in rats with osteoarthritis, potentially by improving cartilage metabolism, regulating the degradation of the extracellular matrix of the articular cartilage, and inhibiting apoptosis in chondrocytes, thereby slowing down joint degeneration^[10]. Limited data, however, has shown the effect of Eucommia on osteonecrosis.

Therefore, to investigate the potential role of Eucommia in the treatment of patients with osteoarthritis and osteonecrosis, we determined the effective rate, the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score, and the levels of bone-GLA protein (BGP), interleukin-17 (IL-17), recombinant human S100 calcium binding protein A12 (S100A12), sphingosine 1-phosphate (SIP), cystatin C (Cysc), creatinine (SCr), and hemoglobin (Hb) in patients with osteoarthritis and osteonecrosis.

MATERIALS AND METHODS

The general information

One-hundred forty osteoarthritis and osteonecrosis cases admitted to Qilu Hospital of Shandong University from January 2013 to December 2017 were selected. Patients were divided into two groups: Eucommia-meloxicam group and meloxicam group. According to the patient case data, there were 70 cases in each group, and there were 94 males and 46 females in the two groups. For osteoarthritis patients, the average age was 65.42 ± 3.38 years. The course of the disease was 3-6 years, with a mean course of disease of 5.17 ± 1.36 years. Regarding location of the disease, there were 32 cases of the left knee and 38 cases of the right knee. For patients with osteonecrosis, the average age was 63.36 ± 4.07 years. The course of the disease was 3-6 years, with a mean course of disease 6.59 ± 1.07 years. There were 33 cases that involved the left knee and 37 cases of the right knee.

Inclusion and exclusion criteria

The inclusion criteria for the guidelines for diagnosis and treatment of osteoarthritis were as follows: (1) Patients met the diagnostic criteria of knee osteoarthritis and medical science imaging diagnosis; (2) Patients conform to the diagnostic criteria of TCM for liver-kidney deficiency and bone; (3) No other relevant treatment was received within 3 mo before enrollment; and (4) One knee disease.

Exclusion criteria were as follows: (1) Complicated fracture, rheumatoid arthritis, other infections, and sexual bone disease; (2) Acute phase of cardiovascular and cerebrovascular events; (3) Malignant tumor; (4) Complications of severe type 2 diabetes present with inability to control stably blood glucose levels; (5) Combination of mental system and psychological diseases, *e.g.*, cognitive impairment; and (6) Bleeding disease, coagulation blood dysfunction; there are contraindications for drugs used in this study in those with certain symptoms and allergic history.

Treatment

The groups included Eucommia-meloxicam group and meloxicam group for osteoarthritis and osteonecrosis. The compound Duzhongjiangu granules was administered as follows: one pack (12 g), three times a day (washed with boiled water after meals) for 1 mo. Meloxicam tablets (15 mg) were taken once a day for 4 wk. *Eucommia ulmoides* Oliver Jiangu granules and meloxicam were obtained from Gansu Minhai Pharmaceutical Co., Ltd (National Drug Approval No.: Z62021048). Meloxicam tablets were obtained from Guangdong Renkang Pharmaceutical Co., LTD (National Drug Approval No.: H20030644).

Clinical efficacy was evaluated according to the evaluation criteria of orthopedic diseases: Total efficacy = (cure + significant + effective)/total cases 100%. The WOMAC score was evaluated: To knee swelling, pain disappeared, knee can be treated freely; Knee pain and swelling were significantly relieved, and knee motion was almost positive; Knee joint disease alleviated, the knee joint movement function changed; There was no improvement in knee joint symptoms after treatment. The disorder is not effective before treatment.

The concentration of the BGP, IL-17, S100A12, SIP, Cysc, SCr, Hb

Patient serum samples stored in Qilu Hospital of Shandong University were used to determine the concentrations of the levels of BGP, IL-17, S100A12, SIP, Cysc, SCr, and Hb by Biochemical analyzer machine and ELISA Kit.

Statistical analysis

Paired *t* test and chi-square test was used to analyze the data using SPSS 21.0 software (Armonk, NY, United States). Statistical significance was defined as a *P* value < 0.05.

RESULTS

The effective rate

In the osteoarthritis experiment, the total effective rate of the Eucommia-meloxicam group and the meloxicam group were 88.57% and 82.85%, respectively. In patients with osteonecrosis, the total effective rate of the Eucommia-meloxicam group and the Meloxicam group were 89.33% and 73.33%, respectively (Table 1 and Table 2).

WOMAC score

WOMAC scores in osteoarthritis patients are shown in Table 3. The scores for pain, stiff, and dysfunction were significantly improved after treatment in both the Eucommia-meloxicam and meloxicam groups ($P < 0.01$). The scores for pain, stiff, and dysfunction between the two groups were compared before and after treatment and were significantly different, except for stiff, in the two groups after treatment ($P < 0.01$).

WOMAC scores in osteonecrosis patients are shown in Table 4. The scores for pain, stiff, and dysfunction were significantly improved after treatment in both the Eucommia-meloxicam and meloxicam groups ($P < 0.01$). The scores of pain, stiff, and dysfunction between the two groups were compared before and after treatment and were significantly different ($P < 0.01$).

The concentration of the BGP, IL-17, S100A12, SIP, Cysc, SCr, Hb

In osteoarthritis patients, the concentration of IL-17, S100A12, SIP, Cysc, SCr, and Hb in the Eucommia-meloxicam group were significantly different before and after treatment ($P < 0.05$). The concentration of BGP, IL-17, S100A12, SIP, Cysc, SCr, and Hb were significantly different in the meloxicam group before and after treatment ($P < 0.01$). The concentration of BGP, IL-17, S100A12, SIP, Cysc, and SCr were significantly different between the two groups before treatment ($P < 0.01$). The concentration of BGP, IL-17, S100A12, SIP, Cysc, SCr, and Hb were significantly different in the two groups after treatment ($P < 0.01$) (Table 5).

In osteonecrosis patients, the concentration of BGP, S100A12, SIP, Cysc, SCr, and Hb were significantly different before and after treatment ($P < 0.05$). The concentration of BGP, IL-17, S100A12, SIP, Cysc, SCr, and Hb were significantly different in the meloxicam group before and after treatment ($P < 0.01$). The concentration of BGP, IL-17, S100A12, SIP, Cysc, and SCr were significantly different between the two groups before treatment ($P < 0.01$) and after treatment ($P < 0.01$) (Table 6).

DISCUSSION

Osteoarthritis is a chronic disease in which the pathological processes start from the catabolism of cartilage extracellular matrix and next extend on the whole joint^[11]. Osteonecrosis is an ischemic pathologic process associated with a number of conditions affecting a range of age groups^[12]. Traditional Chinese medicine has been accepted as a complementary therapy for knee osteoarthritis, not only in Asian countries^[11,13], but also in the West, which might result from its effects on pain, loss of mobility and function, as well as depression.

In this study, the results showed that the total effective rate in the two groups of osteoarthritis was not significantly different, but that the total effective rate in the two groups of osteonecrosis was significantly different. The overall efficacy in the Eucommia-meloxicam group was superior to that in the meloxicam group, indicating that Eucommia can effectively enhance the curative effect of meloxicam.

The WOMAC score data revealed that pain, stiff, and dysfunction in the two groups of osteoarthritis and osteonecrosis before and after treatment were significantly different, indicating that Eucommia and meloxicam can effectively alleviate pain, stiff, and dysfunction in patients with osteoarthritis and osteonecrosis. When comparing WOMAC score of pain between the osteoarthritis and osteonecrosis groups, treatment was significant, indicating that the effect in the Eucommia-meloxicam group was superior to that of the meloxicam group. The combination of Eucommia and meloxicam had a better effect on the osteoarthritis and osteonecrosis than meloxicam alone. Another study by Hussain *et al*^[14] found that meloxicam combined with resveratrol could also alleviate the disease of patients, because it could improve hepatic and renal function and relieve pain, which is consistent with our research results.

The concentration of the S100A12, SIP, Cysc, SCr, and Hb in the Eucommia-meloxicam group and meloxicam group of osteoarthritis and osteonecrosis were

| Table 1 Comparing the two treatment groups for osteoarthritis | | | | |
|---|-------|-----------|---------|-------------------------|
| Item | Cure | Effective | Invalid | Total effective rate, % |
| Eucommia-meloxicam group | 12 | 50 | 8 | 88.57 |
| Meloxicam group | 7 | 51 | 12 | 82.85 |
| χ^2 | 2.126 | | | |
| <i>P</i> value | 0.345 | | | |

significantly different before and after treatment and in the two group of osteoarthritis, the treatments were significant. This finding indicates that *Eucommia* can enhance the effect of meloxicam in patients with osteoarthritis and osteonecrosis and that combining *Eucommia* and meloxicam is better than meloxicam alone.

However, this study still has certain limitations. Firstly, as a retrospective study, a long-term and multi-time point follow-up to the patients was not conducted. Secondly, the mechanism of *Eucommia ulmoides* on osteoarthritis remains unclear. Therefore, we hope to conduct more experiments and include follow-up in future studies to observe further the mechanism of *Eucommia ulmoides* in osteoarthritis, thus supplementing our research results.

Our data indicate that *Eucommia* can effectively enhance the curative effect of meloxicam, and the combination of the *Eucommia* and meloxicam is better than meloxicam alone. It is an effective drug for the treatment of osteoarthritis and osteonecrosis.

Table 2 Comparing the two treatment groups for osteonecrosis

| Item | Effective | Invalid | Total effective rate, % |
|--------------------------|-----------|---------|-------------------------|
| Eucommia-meloxicam group | 67 | 8 | 89.33 |
| Meloxicam group | 55 | 20 | 73.33 |
| χ^2 | 6.323 | | |
| <i>P</i> value | 0.012 | | |

Table 3 Comparison of the WOMAC score in the two groups of osteoarthritis patients

| Item | Time | Pain | Stiff | Dysfunction |
|---|------------------|--------------|-------------|--------------|
| Eucommia-meloxicam group | Before treatment | 13.32 ± 2.12 | 5.23 ± 1.14 | 37.23 ± 3.21 |
| | After treatment | 6.23 ± 1.23 | 2.38 ± 1.06 | 23.35 ± 2.31 |
| | <i>t</i> | 21.266 | 5.544 | 69.158 |
| | <i>P</i> | 0.000 | 0.000 | 0.000 |
| Meloxicam group | Before treatment | 14.42 ± 2.46 | 6.16 ± 1.27 | 36.32 ± 4.17 |
| | After treatment | 3.69 ± 0.37 | 1.85 ± 0.26 | 18.37 ± 3.52 |
| | <i>t</i> | 30.906 | 60.655 | 45.852 |
| | <i>P</i> | 0.000 | 0.000 | 0.000 |
| Comparison of the two groups before treatment | <i>t</i> | 9.179 | 4.418 | 4.876 |
| | <i>P</i> | 0.000 | 0.000 | 0.000 |
| Comparison of the two groups after treatment | <i>t</i> | 21.551 | 0.74 | 11.508 |
| | <i>P</i> | 0.000 | 0.469 | 0.000 |

Table 4 Comparison of the Western Ontario and McMaster Universities Arthritis Index score in the two groups of osteonecrosis

| Item | Time | Pain | Stiff | Dysfunction |
|---|------------------|--------------|-------------|--------------|
| Eucommia-meloxicam group | Before treatment | 16.59 ± 2.13 | 6.84 ± 0.36 | 36.63 ± 4.21 |
| | After treatment | 7.31 ± 3.14 | 1.69 ± 0.23 | 17.42 ± 3.58 |
| | <i>t</i> | 27.141 | 53.830 | 52.858 |
| | <i>P</i> | 0.000 | 0.000 | 0.000 |
| Meloxicam group | Before treatment | 18.31 ± 3.25 | 7.82 ± 0.26 | 35.86 ± 4.36 |
| | After treatment | 5.16 ± 1.59 | 2.42 ± 0.19 | 20.16 ± 3.45 |
| | <i>t</i> | 25.426 | 57.876 | 29.644 |
| | <i>P</i> | 0.000 | 0.000 | 0.000 |
| Comparison of the two groups before treatment | <i>t</i> | 8.643 | 18.094 | 0.751 |
| | <i>P</i> | 0.000 | 0.000 | 0.453 |
| Comparison of the two groups after treatment | <i>t</i> | 11.006 | 12.114 | 12.379 |
| | <i>P</i> | 0.000 | 0.000 | 0.000 |

Table 5 Comparison of the two treatment groups for osteoarthritis

| Item | | BGP | IL-17 | S100A12 | SIP | Cysc | SCr | Hb |
|------------------------------|------------------|-------------|---------------|--------------|--------------|-------------|----------|-------------|
| Eucommia and meloxicam group | Before treatment | 2.12 ± 0.12 | 152 ± 6.13 | 43 ± 3.2 | 0.23 ± 0.05 | 0.83 ± 0.3 | 46 ± 4.2 | 132 ± 8.9 |
| | After treatment | 1.88 ± 0.35 | 136.44 ± 4.58 | 36.37 ± 5.68 | 0.116 ± 0.05 | 1.12 ± 0.5 | 63 ± 3.6 | 113 ± 12.1 |
| | <i>t</i> | 2.228 | 6.4 | 4.008 | 6.334 | 3.894 | 10.17 | 2.55 |
| | <i>P</i> | 0.053 | 0.000 | 0.003 | 0.000 | 0.004 | 0.000 | 0.031 |
| Meloxicam group | Before treatment | 0.87 ± 0.21 | 125 ± 6.4 | 32 ± 6.3 | 0.11 ± 0.05 | 0.87 ± 0.43 | 53 ± 4.9 | 124 ± 3.6 |
| | After treatment | 0.64 ± 0.19 | 104 ± 6.4 | 18 ± 3.4 | 0.057 ± 0.01 | 1.46 ± 0.42 | 74 ± 5.7 | 104.3 ± 6.8 |
| | <i>t</i> | 3.915 | 7.848 | 5.609 | 5.331 | 3.155 | 15.374 | 10.632 |
| | <i>P</i> | 0.004 | 0.000 | 0.000 | 0.000 | 0.012 | 0.000 | 0.000 |

| | | | | | | | | |
|---|----------|--------|--------|-------|-------|-------|-------|-------|
| Comparison of the two groups before treatment | <i>t</i> | 30.644 | 12.747 | 5.827 | 6.357 | 3.399 | 7.23 | 2.215 |
| | <i>P</i> | 0.000 | 0.000 | 0.000 | 0.000 | 0.008 | 0.000 | 0.054 |
| Comparing the two groups after treatment | <i>t</i> | 35.845 | 14.523 | 8.409 | 3.174 | 2.774 | 4.97 | 2.456 |
| | <i>P</i> | 0.000 | 0.000 | 0.000 | 0.011 | 0.022 | 0.000 | 0.036 |

BGP: Bone-GLA protein; S100A12: Recombinant human S100 calcium binding protein A12; SIP: Sphingosine 1-phosphate; Cysc: Cystatin C; SCr: Creatinine; Hb: Hemoglobin.

Table 6 Comparison of the two treatment groups for osteonecrosis

| Item | | BGP | IL-17 | S100A12 | SIP | Cysc | SCr | Hb |
|---|------------------|-------------|----------------|-------------|---------------|-------------|----------|-----------|
| Eucommia and meloxicam group | Before treatment | 1.95 ± 0.17 | 142 ± 11.56 | 65 ± 4.6 | 0.312 ± 0.06 | 2.45 ± 0.21 | 35 ± 5.3 | 145 ± 6.4 |
| | After treatment | 1.64 ± 0.15 | 125.13 ± 13.84 | 42.7 ± 4.8 | 0.124 ± 0.04 | 1.42 ± 0.17 | 57 ± 3.5 | 123 ± 4.6 |
| | <i>t</i> | 2.419 | 1.432 | 7.924 | 9.185 | 8.175 | 12.513 | 6.713 |
| | <i>P</i> | 0.039 | 0.186 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| Meloxicam group | Before treatment | 0.85 ± 0.13 | 123 ± 8.5 | 53 ± 4.7 | 0.132 ± 0.004 | 2.13 ± 0.11 | 68 ± 5.4 | 132 ± 5.4 |
| | After treatment | 0.58 ± 0.21 | 98.1 ± 12.9 | 16.38 ± 3.5 | 0.069 ± 0.005 | 1.69 ± 0.19 | 82 ± 3.5 | 105 ± 4.7 |
| | <i>t</i> | 3.723 | 3.517 | 14.093 | 5.506 | 4.856 | 5.239 | 13.069 |
| | <i>P</i> | 0.005 | 0.007 | 0.000 | 0.000 | 0.001 | 0.001 | 0.000 |
| Comparison of the two groups before treatment | <i>t</i> | 15.74 | 7.292 | 3.17 | 8.95 | 4.848 | 10.548 | 5.745 |
| | <i>P</i> | 0.000 | 0.000 | 0.011 | 0.000 | 0.001 | 0.000 | 0.000 |
| Comparison of the two groups after treatment | <i>t</i> | 11.959 | 10.409 | 9.833 | 4.25 | 4.013 | 12.444 | 9.21 |
| | <i>P</i> | 0.000 | 0.000 | 0.000 | 0.002 | 0.003 | 0.000 | 0.000 |

BGP: Bone-GLA protein; S100A12: Recombinant human S100 calcium binding protein A12; SIP: Sphingosine 1-phosphate; Cysc: Cystatin C; SCr: Creatinine; Hb: Hemoglobin.

ARTICLE HIGHLIGHTS

Research background

Osteoarthritis is a multifactorial disease and its occurrence is positively related to age and is the leading cause of disability and pain.

Research motivation

There is currently no effective pharmacological strategy to prevent the development of the disease.

Research objectives

To evaluate the therapeutics of the compound Eucommia bone tonic granules for treating osteoarthritis and osteonecrosis.

Research methods

Patients were separated into two treatment groups: the Eucommia-meloxicam group and the meloxicam group. In addition, the concentrations of bone-GLA protein, interleukin-17, recombinant human S100 calcium binding protein A12, Sphingosine 1-phosphate, cystatin C, creatinine, and hemoglobin were compared before and after treatment. The bone and joint necrosis test and osteonecrosis experiment were carried out to observe the total effective rate of the two groups.

Research results

The combination of Eucommia and meloxicam treatment resulted in improved pain relief and patient satisfaction.

Research conclusions

The combination of Eucommia and meloxicam was an effective and safe drug in the treatment of osteoarthritis and osteonecrosis.

Research perspectives

The patients with osteoarthritis and osteonecrosis will receive benefits from the latest innovations in drug therapies.

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