Efficacy and Safety of Zhuanggu Joint Capsules in Combination with Celecoxib in Knee Osteoarthritis: A Multi-center, Randomized, Double-blind, Double-dummy, and Parallel Controlled Trial

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Abstract

Background: Knee osteoarthritis (KOA) is a chronic joint disease that manifests as knee pain as well as different degrees of lower limb swelling, stiffness, and movement disorders. The therapeutic goal is to alleviate or eliminate pain, correct deformities, improve or restore joint functions, and improve the quality of life. This study aimed to evaluate the efficacy and safety of Zhuanggu joint capsules combined with celecoxib and the benefit of treatment with Zhuanggu alone for KOA.

Methods: This multi-center, randomized, double-blind, double-dummy, parallel controlled trial, started from December 2011 to May 2014, was carried out in 6 cities, including Beijing, Shanghai, Chongqing, Changchun, Chengdu, and Nanjing. A total of 432 patients with KOA were divided into three groups (144 cases in each group). The groups were treated, respectively, with Zhuanggu joint capsules combined with celecoxib capsule simulants, Zhuanggu joint capsules combined with celecoxib capsules, and celecoxib capsules combined with Zhuanggu joint capsule simulants for 4 weeks consecutively. The improvement of Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index and the decreased rates in each dimension of WOMAC were evaluated before and after the treatment. Intergroup and intragroup comparisons of quantitative indices were performed. Statistically significant differences were evaluated with pairwise comparisons using Chi-square test (or Fisher’s exact test) and an inspection level of \( \alpha = 0.0167 \).

Results: Four weeks after treatment, the total efficacies of Zhuanggu group, combination group, and celecoxib group were 65%, 80%, and 64%, respectively, with statistically significant differences among the three groups (\( P = 0.005 \)). Intergroup pairwise comparisons showed that the total efficacy of the combination group was significantly higher than that of the Zhuanggu (\( P = 0.005 \)) and celecoxib (\( P = 0.003 \)) groups. The difference between the latter two groups was not statistically significant (\( P > 0.0167 \)). Four weeks after discontinuation, the efficacies of the three groups were 78%, 95%, and 65%, respectively, with statistically significant differences (\( P < 0.0001 \)). Intergroup pairwise comparisons revealed that the efficacy of the combination group was significantly better than that of the Zhuanggu and the celecoxib groups (\( P < 0.0001 \)). The difference between the latter two groups was not statistically significant (\( P > 0.0167 \)). The incidences of adverse events in Zhuanggu group, combination group, and celecoxib group were 8.5%, 8.5%, and 11.1%, respectively, with insignificant differences (\( P > 0.05 \)).

Conclusions: Zhuanggu joint capsules alone or combined with celecoxib showed clinical efficacy in the treatment of KOA. The safety of Zhuanggu joint capsules alone or combined with celecoxib was acceptable.
**Key words:** Celecoxib; Drug Combination; Knee Osteoarthritis; Zhuanggu Joint Capsule

**Introduction**

Osteoarthritis (OA) is one of the most common diseases affecting human health, especially the health of the elderly, worldwide. It is one of the major diseases inducing functional impairment in population aged 50 years and older, resulting in economic loss and poor social development.\(^1\) Knee OA (KOA) is a chronic joint disease, involving articular cartilage, synovial joint capsule, and muscles around the joint. The irreversible damage manifests as knee pain as well as different degrees of lower limb swelling, stiffness, and movement disorders.\(^2\) Currently, the therapeutic goal of OA is to alleviate or eliminate pain, correct deformities, improve or restore joint functions, and improve the quality of life.\(^3\) Nonsteroidal anti-inflammatory drugs (NSAIDs), which tend to relieve symptoms temporarily, are widely used in clinical practice. Adverse reactions in the gastrointestinal tract, kidney, and central nervous system caused by NSAIDs have been reduced using a new generation of NSAIDs, such as celecoxib and rofecoxib. However, the risk of cardiovascular toxicity remains.\(^2\)

Zhuanggu joint capsules are used to invigorate liver and kidney, nourish and activate blood, stimulate blood circulation, and relax the muscles and joints, as well as regulate vital energy and alleviate pain. In this study, we evaluated the efficacy and safety of a combination of Zhuanggu joint capsules and celecoxib compared with celecoxib alone, and explored the therapeutic efficacy of Zhuanggu joint capsules in ameliorating the symptoms and signs of KOA.

**Methods**

This multi-center, randomized, double-blind, double-dummy, and parallel controlled trial was led by Shanghai No. 6 People’s Hospital, and conducted between December 2011 and May 2014, involving the following hospitals: West China Hospital, Southwest Hospital, No. 1 Hospital of Jinlin University, Shanghai Tenth People’s Hospital, The First Affiliated Hospital of Nanjing Medical University, Beijing Hospital, Shanghai No. 1 People’s Hospital, and Peking Union Medical College Hospital (consultant and protocol design). This study was approved by the Ethics Committee of Shanghai No. 6 People’s Hospital (No. 2012-35-1). All the patients had written the informed consent to undergo drug therapy consistent with Good Clinical Practice (GCP) requirements.

**Patients**

**Number of cases**

The Phase IV trial involving 2149 patients conducted by China Resources Sanjiu Medical & Pharmaceutical Co., Ltd., between September 2004 and October 2006 showed a 62% efficacy of Zhuanggu joint capsules in KOA. The efficacy of celecoxib capsules in the multi-center, randomized, double-blind, positive drug, and placebo-controlled study involving 1583 patients conducted by Clegg et al.\(^4\) was 70%. The estimated efficacy of the combination treatment comprising Zhuanggu and celecoxib capsules was 80%. The sample size was estimated using two-sided test of difference using a ratio of test group 1: test group 2: control group of 1:1:1, and \(\alpha = 0.05, \beta = 0.20\) (certainty of 80%). A sample size of 120 cases in each group was obtained. The quality of the study was strictly controlled during the testing process. The follow-up loss rate was below 20%, including a total of 432 cases, with 144 cases in each group, implying that each study center included 54 cases.

**Inclusion criteria**

1. Age 40–70 years, male or female; (2) diagnostic criteria of KOA,\(^4,5\) with X-ray Kellgren–Lawrence classification ≤grade III; (3) normal liver and renal function; (4) written informed consent to undergo drug therapy consistent with GCP requirements.

**Exclusion criteria**

1. Acute joint injury, tuberculosis and tumors of the knee joints, and rheumatoid arthritis; (2) severe cardiovascular, metabolic, digestive, urinary, neurological, and psychiatric disorders, or exclusion by the investigators; (3) prohibited drug intake or need to continue the usage of prohibited drugs during the trial; (4) history of study drug intake within one month or participation in the clinical trials of drugs; (5) lactating and pregnant women or women of childbearing age contemplating pregnancy; (6) contraindications to Zhuanggu or NSAIDs; (7) susceptibility or allergy to the components of study drugs; (8) staff directly involved in this trial or relatives of staff; and (9) alcohol and/or drug abuse or poor compliance.

**Rejection criteria**

1. Misdiagnosis or errors in study enrolment; (2) inconsistency with the inclusion criteria or consistency with the exclusion criteria upon recheck; (3) medication nonadherence; (4) absence of any test record; and (5) inability to test efficacy due to the use of prohibited drugs.

**Drugs**

Zhuanggu joint capsules (specification: 0.45 g/grain, lot number: 1202001S) and Zhuanggu joint capsule simulant (specification: 0.45 g/grain, lot number: 1202071) were produced by China Resources Sanjiu Medical & Pharmaceutical Co., Ltd. Celecoxib capsules (Celebrex, specification: 0.2 g/grain, lot number: 1100323) were produced by Pfizer Pharmaceuticals Ltd. The celecoxib
capsule simulant (specification: 0.2 g/grain, lot number: 1202081) was produced by China Resources Sanjiu Medical & Pharmaceutical Co., Ltd.

**Trial protocol**

**Trial design**

In this multi-center, randomized, double-blind, double-dummy, parallel controlled trial, the eligible patients were randomized using random number table into three groups: Zhuanggu group, celecoxib group, and combination group. The predicted subject numbers in each site was an integral multiple of the randomized block.

**Treatment regimen**

The combination group was administered Zhuanggu plus celecoxib capsules; Zhuanggu group was given Zhuanggu joint capsules plus celecoxib capsule simulant; and the celecoxib group was given Zhuanggu joint capsule simulant combined with celecoxib capsules, administered with two grains of Zhuanggu, twice-daily, after meal in the morning and evening. A grain of celecoxib capsule was administered, once-daily. The treatment duration was 4 weeks, with a face-to-face follow-up visit 4 weeks after completion. The administration and dosage of the simulants were similar to those of the corresponding drugs.

**Outcomes and evaluation criteria**

**Primary outcomes**

The Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index (assessed at enrollment, end of 2nd week of treatment, end of treatment, and end of follow-up) was used to assess the joints within 48 h, with zero suggesting asymptomatic (difficult), 1 denoting mild, 2 suggesting equal, 3 indicating very much, and 4 representing extreme conditions. The reduction rate was calculated as: (total pretreatment score − total posttreatment score)/total pretreatment score × 100%. The term “clinically controlled” refers to a WOMAC score ≥75%; “significantly improved” indicates a WOMAC score ≥50%, but <75%; “improved” suggests a WOMAC score ≥25%, but <50%; and “ineffective” referred to a WOMAC score <25%. Efficacy was calculated as: (“clinically controlled” + “significantly improved”)/total number of cases × 100%.

**Secondary outcomes**

Secondary outcomes included a comparison of reduction rates in various dimensions of the WOMAC scale.

**Safety indices**

Safety indices included vital signs; physical examination; routine blood and urine tests; liver function (alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, glutamate transpeptidase), kidney function (blood urea nitrogen and creatinine) and electrocardiogram tests; and adverse events.

**Statistical analysis**

Statistical analyses were performed using SAS 9.13 software (SAS Institute Inc., USA). Categorical data were expressed as percentages or constituent ratios. Continuous data were expressed as mean ± standard deviation (SD) or median (minimum, maximum). Intergroup comparisons were performed using Chi-square test (or Fisher’s exact test) or analysis of variance or rank sum test. All the tests were performed using a two-sided test of difference, where the inspection level $\alpha$ of 0.05 and a difference with $P < 0.05$ were considered statistically significant. Pairwise comparisons among the three groups were corrected by Bonferroni method, with the corrected inspection level, i.e., $\alpha$ of 0.0167.

**Results**

**General information**

In this study, 429 cases were actually enrolled (142, 143, and 144 cases in the Zhuanggu, combination, and celecoxib groups, respectively). Of these cases, 414 were enrolled in the full analysis set (136, 138, and 140 cases in the three groups, respectively). A total of 395 cases (132, 132, and 131 cases in the three groups, respectively) were included in the per-protocol set analysis and 428 cases (142, 142, and 144 cases in the three groups, respectively) were included in the security data set analysis.

**Efficacy assessment**

**Baseline analysis**

1. Demographic analysis: Ages of participants when they entered the group were 55 ± 7 years in Zhuanggu group, 55 ± 8 years in combination group, and 56 ± 8 years in celecoxib group. There was no statistically significant difference among these groups in gender, ethnicity, age, height, weight, allergy history ($P > 0.05$) etc., in which case they could be compared with each other [Table 1].

2. Systematic physical examination analysis: No significant difference could be found among the three groups in skin, head and neck, facial features, respiration, cardiovascular system ($P > 0.05$). Thus, they could be compared with each other [Table 2].

3. Analysis on diagnostic history, treatment history, etc.: There were around 80% of patients whose knee joint X-ray was classified as level I and level II for the three groups, without any statistically significant difference ($P > 0.05$). Median disease course was 9 months for Zhuanggu joint capsules group, whereas 8 months for combined drug group, and 9 months for celecoxib group, without any statistically significant difference ($P > 0.05$). Differences in treatment history and complicated diseases had no statistical significance ($P > 0.05$). Thus, the above indicators could be compared with each other [Table 3].

4. Analysis on the effectiveness of baseline information: before treatment, WOMAC score was 23 ± 8 for Zhuanggu group, 22 ± 8 for combination group, and 23 ± 9 for celecoxib group, without statistically significant difference ($P > 0.05$). Differences in the score of three dimensions, including pain, stiffness, and difficult in daily activities, had no statistical
The above results showed that WOMAC score could be compared between different groups [Table 4].

**Primary outcomes**

1. Comparison of two-category efficacy of WOMAC reducing rate: Four weeks after treatment, the efficacies of the three groups were 65%, 80%, and 64%, respectively, with statistically significant differences among the three groups ($P = 0.005$). Intergroup pairwise comparisons showed that the total efficacy of the combination group was higher than that of the Zhuanggu ($P = 0.005$) and celecoxib ($P = 0.003$) groups, with statistically significant differences. The difference between the latter two groups was not statistically significant ($P > 0.0167$).

Four weeks after discontinuation, the efficacies of the different groups were 78%, 95%, and 65%, respectively, with statistically significant differences ($P < 0.0001$). Intergroup pairwise comparisons revealed that the efficacy of the combination group was better than that of the Zhuanggu group ($P = 0.005$) and celecoxib group ($P = 0.003$), with statistically significant differences. The difference between the latter two groups was not statistically significant ($P > 0.0167$).
Zhuanggu and the celecoxib groups \((P < 0.0001)\), with statistically significant differences. The difference between the latter two groups was not statistically significant \((P > 0.0167)\) [Table 5].

2. Comparison of four-category efficacy of WOMAC reducing rate: Four weeks after the treatment, the differences in efficacy among the three groups were statistically significant \((P = 0.0004)\). Intergroup pairwise comparisons revealed that the efficacy of the combination group was better than that of the Zhuanggu \((P = 0.0003)\) and celecoxib \((P = 0.001)\) groups. The difference between the latter two groups was not statistically significant \((P > 0.0167)\) [Table 5].

### Secondary outcomes

1. Pain score: Four weeks after treatment, the pain score was significantly decreased by 54% ± 26%, 72% ± 24%, and 68% ± 27% in the three groups, respectively \((P < 0.0001)\). Further, pairwise comparisons reveal that the pain scores in the combination group \((P < 0.0001)\) and the celecoxib group \((P = 0.0002)\) were better than that of the Zhuanggu group, while the differences between the combination group and celecoxib group was statistically insignificant \((P > 0.0167)\) [Table 6].

### Tables

| Table 3: Baseline analysis on diagnostic and treatment history of patients with knee osteoarthritis in three groups |
|---|
| Index | Zhuanggu group \((n = 136)\) | Combination group \((n = 138)\) | Celecoxib group \((n = 140)\) | Statistics | \(P\) |
| Knee joint X-ray (miss = 0), n (%) | | | | 0.68* | 0.710 |
| Level 0 | 7 (5) | 13 (9) | 10 (7) | | |
| Level I | 60 (44) | 57 (41) | 65 (46) | | |
| Level II | 56 (41) | 56 (41) | 53 (38) | | |
| Level III | 13 (10) | 12 (9) | 12 (9) | | |
| Disease course (months), median (minimum, maximum) | 9 (1, 480) | 8 (1, 480) | 9 (1, 300) | 0.86* | 0.649 |
| Treatment history (miss = 0), n (%) | | | | 1.23† | 0.542 |
| No | 113 (83) | 121 (88) | 118 (84) | | |
| Yes | 23 (17) | 17 (12) | 22 (16) | | |
| Complicated disease (miss = 0), n (%) | | | | 0.68† | 0.713 |
| No | 121 (89) | 121 (88) | 120 (86) | | |
| Yes | 15 (11) | 17 (12) | 20 (14) | | |

*: \(Z\) values; †: \(\chi^2\) values.

| Table 4: Baseline analysis on WOMAC score of patients with knee osteoarthritis in three groups |
|---|
| Index | Zhuanggu group \((n = 136)\) | Combination group \((n = 138)\) | Celecoxib group \((n = 140)\) | \(F\) | \(P\) |
| WOMAC score, mean ± SD | 23 ± 8 | 22 ± 8 | 23 ± 9 | 0.79 | 0.456 |
| Pain score, mean ± SD | 6 ± 2 | 5 ± 2 | 6 ± 2 | 0.86 | 0.424 |
| Stiffness score, mean ± SD | 1 ± 1 | 1 ± 1 | 1 ± 1 | 1.42 | 0.243 |
| Difficulty in daily activities, mean ± SD | 17 ± 6 | 16 ± 6 | 16 ± 6 | 0.43 | 0.653 |

WOMAC: Western Ontario and McMaster Universities Osteoarthritis; SD: Standard deviation.

| Table 5: Two-category analysis of WOMAC reduction of patients with knee osteoarthritis in three groups |
|---|
| Index | Zhuanggu group \((n = 136)\) | Combination group \((n = 138)\) | Celecoxib group \((n = 140)\) | \(\chi^2\) | \(P\) |
| Efficacy at week 4, n (%) | | | | 10.69 | 0.005 |
| Inefficacy | 47 (35) | 27 (20) | 50 (36) | | |
| Efficacy | 89 (65) | 111 (80) | 90 (64) | | |
| Efficacy at week 8, n (%) | | | | 38.02 | <0.0001 |
| Inefficacy | 30 (22) | 7 (5) | 49 (35) | | |
| Efficacy | 106 (78) | 131 (95) | 91 (65) | | |

WOMAC: Western Ontario and McMaster Universities Osteoarthritis.
Table 6: Four-category analysis of WOMAC reduction of patients with knee osteoarthritis in three groups

| Index                  | Zhuanggu group (n = 136) | Combination group (n = 138) | Celecoxib group (n = 140) | Z    | P   |
|------------------------|--------------------------|-----------------------------|---------------------------|------|-----|
| Efficacy at week 4, n (%) |                          |                             |                           |      |     |
| Ineffectve             | 14 (10)                  | 3 (2)                       | 15 (11)                   | 15.50| 0.0004|
| Improved               | 33 (24)                  | 24 (17)                    | 35 (25)                   |      |     |
| Significantly improved  | 66 (49)                  | 67 (49)                    | 60 (43)                   |      |     |
| Clinically controlled   | 23 (17)                  | 44 (32)                    | 30 (21)                   |      |     |
| Efficacy at 8 weeks, n (%) |                          |                             |                           | 51.39| <0.0001|
| Ineffectve             | 7 (5)                    | 2 (1)                       | 15 (11)                   |      |     |
| Improved               | 23 (17)                  | 5 (4)                      | 34 (24)                   |      |     |
| Significantly improved  | 77 (57)                  | 69 (50)                    | 68 (49)                   |      |     |
| Clinically controlled   | 29 (21)                  | 62 (45)                    | 23 (16)                   |      |     |

WOMAC: Western Ontario and McMaster Universities Osteoarthritis.

differences among the groups (P < 0.0001). Pairwise comparisons revealed that the pain reduction in the combination group was better than that of the Zhuanggu group (P < 0.0001) and celecoxib group (P = 0.004), although the difference between the latter two groups was not statistically significant (P > 0.0167).

2. Stiffness score reduction: Four weeks after treatment, the decrease in the rate of stiffness was not significantly different among the three groups (P > 0.05), while the differences at 4 weeks after discontinuation were significant (P < 0.05). However, no significant differences in efficacy were observed by pairwise comparisons (P > 0.0167).

3. Decreased difficulty of daily activity: Four weeks after treatment, the rate of difficulty with activity was decreased by 54% ± 22%, 64% ± 19%, and 53% ± 21% in the three groups, respectively, with statistically significant intergroup differences (P < 0.0001). Further, pairwise comparisons showed that the decreased difficulty of daily activity in the combination group was better than in the Zhuanggu (P = 0.0004) and celecoxib groups (P < 0.0001), the difference between the latter two groups was not statistically significant (P > 0.0167). Four weeks after discontinuation, the rate of difficulty in daily activity decreased by 60% ± 21%, 71% ± 18%, and 51% ± 21% in the three groups, respectively, with significant differences (P < 0.0001). The pairwise comparison revealed that the efficacy of the combination group was better than that of the Zhuanggu group (P < 0.0001) and the celecoxib group (P < 0.0001), while the efficacy of the Zhuanggu joint capsules was better than that of the celecoxib capsules (P = 0.0009).

Assessment of safety

In this study, a total of 54 adverse events occurred in 40 patients. The events included diarrhea, bellyache, stomachache, erythrasma, allergy, and abnormal liver function. A total of 19 adverse events occurred in 12 patients in the Zhuanggu group, with an 8.5%, and 16 adverse events occurred in 12 patients in the combination group, with an incidence of 8.5%, whereas 19 adverse events occurred in 16 patients in the celecoxib group, with an incidence of 11.1%. The incidence of adverse events was not significantly different among the three groups (P > 0.05).

Discussion

KOA is a chronic joint disease, which is mostly occurred in middle-aged and elderly people and mainly caused by degenerative changes of cartilage and secondary bone hyperplasia. It is the most common bone metabolic disease in addition to osteoporosis. It is always the main cause which leads disability in adults and a serious threat to human health. Senility, obesity, trauma, strain, and genetics are all its pathogenic factors, but its pathogenesis is not clear until now. The pathological feature is the degeneration of articular cartilage, and the cells of degenerated cartilage are mainly fibroblast chondrocytes and hypertrophic chondrocytes. At the same time, it also involves the whole joint including cartilage, ligament, joint capsule, synovial membrane, and joint surrounding muscles, which eventually cause joint pain, joint stiffness, joint dysfunction, and other behavioral disorders. For patients with advanced KOA, surgical treatment is often required, including autologous bone cartilage transplantation under arthroscopy and total knee arthroplasty. However, surgery not only brings great physical and mental pain to patients, but also causes heavy economic burden. Currently, by suppressing the activity of cyclooxygenase (COX), NSAIDs can suppress the production of prostacyclin from arachidonic acid to relieve pain. Moreover, it is a common medicine used to treat arthritis. Celecoxib is a COX-2 inhibitor, and it has been sold in China for many years. This drug has exact efficacy in treating arthritis with little side effects, in which case it has been widely used.

In the theory of traditional Chinese medicine, KOA’s progression is due to the interaction and the mutual promotion of internal and external factors. The internal factors are the deficiency of liver and kidney. The external factors are Qi stagnation, blood stasis, and meridian blockage. The components of Zhuanggu joint capsules are exactly aimed at KOA’s internal and external factors, so
it can quickly improve the function and ease the pain. The medicine has advantages such as fewer side effects, shorter course of treatment, and lower price.

In this study, a follow-up of 4 weeks after discontinuation, based on the WOMAC and daily activity difficulty scores, it was shown that the combination therapy had long-term benefits. However, since patients were allowed to take celecoxib capsules during the follow-up after discontinuation, we failed to obtain the drug dosage and were unable to determine if this long-term effect was associated with ongoing drug administration.

The efficacy and safety assessments in 2149 patients receiving Zhuanggu confirmed the safety of the intervention. The safety was also consistent with application of celecoxib alone. However, previous studies revealed that these two therapies were associated with adverse reactions. The adverse reactions of Zhuanggu included dry mouth and transient elevation in amino transferase levels, whereas those of the celecoxib capsules manifested as adverse cardiovascular events, especially in middle-aged and elderly patients. The safety of the combination treatment was not significantly different compared with monotherapy, and therefore, was acceptable to patients.

In summary, Zhuanggu joint capsules alone or combined with celecoxib were clinically efficacious in the treatment of KOA. However, the efficacy was superior with the combination therapy. The safety of Zhuanggu joint capsules alone or combined with celecoxib was acceptable.

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Conflicts of interest
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