

Full Length Research Paper

Comparative study of drug intervention in treatment of rural middle-aged and elderly people with knee osteoarthritis in Fengxian District, Shanghai

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The aim of this study is to perform intervention treatment with loxoprofen, diacerein and glucosamine for middle-aged and elderly knee osteoarthritis (KOA) patients and compare the efficacy and safety of the aforementioned three drugs on KOA as well as providing basis for standard treatment protocol for the exploration of KOA. 153 KOA patients who were proved in the project of KOA epidemiological survey on rural middle-aged and elderly people in Fengxian District, Shanghai City were taken as the subject of study. Random, open and self-control methods were adopted to conduct intervention treatment by dividing into three groups: loxoprofen, diacerein and glucosamine treatment group. Evaluation method for index of severity and activity of KOA by lequesne was referred to make follow-up visit, fill in questionnaire on drug adverse reaction, registration form of drug distribution and recycle. Intervention treatments with loxoprofen, diacerein and glucosamine were carried out for KOA patients and significant differences ($p < 0.05$) were seen between self-control groups in the aspect of knee pain, 15 m walking time (t/s), activities of daily life and comprehensive evaluation for patient. The overall response rates of the drug intervention in three groups are 90.20, 74.51 and 88.24%, respectively with $R(-)_1 = 0.4424$, $R(-)_2 = 0.5825$ and $R(-)_3 = 0.4751$ by Ridit analysis. Considering $\chi^2 = 6.7253$, $p < 0.05$, the efficacy of loxoprofen and glucosamine turned out to be better, followed by that of diacerein; the adverse reaction of the three drugs are quite slight. With certain efficacy for KOA and slight adverse reaction, the intervention treatment of loxoprofen, diacerein and glucosamine can be used for normalized treatment of KOA. The use of drug intervention treatment can postpone the progression of KOA.

Key words: Rural area, knee osteoarthritis, drug intervention.

INTRODUCTION

Knee osteoarthritis (KOA) is a kind of degenerative joint disease with a markedly increasing incidence along with age. It is the most common joint disease as well the most common causes leading to joint pain of middle-aged and elderly people, thus affecting the quality of middle-aged and elderly people's lives seriously. Currently, the drug treatment of KOA mainly adopts Nonsteroidal Anti-inflammatory Drugs (NSAIDs), which is widely applied clinically due to its effectiveness in the treatment of rest pain, nocturnal pain and inflammatory pain (McCarberg

and Herr, 2001). To probe into some drugs with reliable efficacy, little side effects and low price as well as list them as normalized treatment protocol, based on the random samples of incidence and epidemiologic feature of KOA in rural middle-aged and elderly people in Fengxian District, Shanghai City. The included KOA patients were randomly divided into different groups for drug intervention treatment of loxoprofen, diacerein and glucosamine.

SUBJECTS AND METHODS

157 KOA patients, who were proved by KOA epidemiological survey for rural middle-aged and elderly people in Fengxian District of

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Table 1. Distribution of height and weight etc. of rural middle-aged and elderly people with KOA in Fengxian District.

Item	Male (45 patients)	Female (108 patients)
Height (cm)	166.08±5.37	156.04±8.84
Weight (kg)	64.11±9.69	57.33±9.38
Body mass index (kg/m ²)	23.20±3.01	23.43±3.51

Table 2. Distribution of gender, age and average course of disease for rural middle-aged and elderly people with KOA in Fengxian District.

Group	Gender		Age	Average course of disease (month)	X-ray stages		
	Male	Female			I	II	III
Loxoprofen	15	36	54.21±11.23	14.2±12.2	21	22	8
Diacerein	14	37	56.42±12.02	15.8±14.3	20	21	10
Glucosamine	16	35	56.38±10.14	14.8±11.4	18	24	9
<i>P</i> value	>0.05		>0.05	>0.05	>0.05		

Shanghai City, were included as the objects of study (Wang et al., 2008), among whom 3 patients were excluded from the study due to alimentary tract active ulcer and 1 patient refused to participate in intervention treatment. Among 153 patients who were volunteered to participate in the intervention treatment, there are 45 men and 108 women with a proportion of 1:2.40. The average ages of men and women were (56.12±9.42) and (57.6±10.3), respectively. Their height, weight and basic situations could be seen in Table 1.

153 KOA patients without receiving glucocorticoid treatment nor viscera diseases such as heart, liver and kidney and alimentary tract active ulcer within a month. Kellgren/Lawrence grading (Kellgren and Lawrence, 1957) was used to evaluate knee joint radiography. 153 KOA patients were randomly divided into three groups: Loxoprofen, diacerein and glucosamine. Gender, age and average course of disease and X-ray staging among groups are comparable (Table 2).

Drug intervention

Random, open and self-control test are adopted in drug intervention treatment, in which patients in loxoprofen group were given loxoprofen tablet at the dosage of 60 mg, 1#tid, course of treatment: 3 weeks; the patients in diacerein group were given diacerein tablets at the dosage of 50 mg, 1#bid, course of treatment: 3 months; while the patients in glucosamine group glucosamine tablets at the dosage of 454 mg, 2#tid, course of treatment: 3 months by referring to relevant evaluation on severity and active index of KOA by Lequensne (1991). Records were made before and after administration. Evaluation of knee activity-related pain (10 cm visual analogue scale is adopted), 15 m walking time (t/s), joint tenderness, activities of daily living (go upstairs and squat). Meanwhile, observations and records was made on whether there are major adverse reactions such as anorexia, epigastria pain, diarrhoea, astriction, upper gastrointestinal hemorrhage, bad breath, rash and edema during the period of drug administration. The administration was discontinued for patients with severe adverse reactions.

Two photos of the double knee joints of KOA patients in anteroposterior and lateral position before and after intervention treatment was taken respectively. The X ray photo adopts the unified conditions for photos, the unified combination of high speed sense green film, and the unified photo specification and size (10 × 12 cm). The position of the image result was from 1/4 of the lower

thighbone to 1/4 of the upper tibiofibula, while the patella is located on 1/3 of the whole film. X-ray photos conformed to the requirements of clinical diagnosis and quality standard for x-ray diagnosis. X-ray film was conducted by two physicians from the Radiology Department, who were not familiar with the clinical situation, and 20 to 30% X ray film was extracted and re-read. Radiodiagnosis adopts kellgren/Lawrence (k/L) grading criteria (Kellgren and Lawrence, 1957), which are divided into Grade 0 to 4: Grade 0 stands for normal; Grade 1 stands for possible hyperosteogeny; Grade 2 stands for definite hyperosteogeny; Grade 3 stands for moderate hyperosteogeny and/or explicit stenosis of joint space; Grade 4 stands for severe hyperosteogeny, explicit stenosis of joints space and/or articular surface of sclerosis.

Efficacy evaluation

Evaluation was made in this study in accordance with the Guideline for Clinical Study on Drugs in Treatment of Rheumatism: Comprehensive Evaluation of the Efficacy of Anti-inflammatory Drugs. The criteria for efficacy evaluation are:

- (1) Invalid: Clinical symptoms, sign and laboratory index were improved to <30%;
- (2) Improved: Clinical symptoms, sign and laboratory index were improved from 30 to 50%;
- (3) Progression: Clinical symptoms, sign and laboratory index were improved from 51 to 74%;
- (4) Remarkable progression: Clinical symptoms, sign and laboratory index were improved to ≥75%.

The overall response rate (%) = [(Improvement + progression+ remarkable progression) × number of patients] / total number of patients × 100%.

Statistical analysis

The SPSS 16.0 software package for Windows was used for all statistical analysis. Data were represented as mean ± S.D. The two–two comparisons of the efficacy between pretreatment and pretreatment were performed by paired *t*-test. Redit analysis was applied in comparison of efficacy. χ^2 test was used for comparison of enumeration data and Kruskal-Wallis test for measurement data and ranked data. $p < 0.05$ was considered as statistically significant.

Table 3. Situation of rural middle-aged and elderly people with KOA in Fengxian District.

Age	Male			Female			χ^2 value	P value
	Number of people	Number of patients	Morbidity rate (%)	Number of people	Number of patients	Morbidity rate (%)		
~27	125	6	4.8	143	8	5.59	0.085	>0.05
~50	137	18	13.14	220	44	20	2.77	>0.05
~60	65	11	16.92	85	39	45.88	13.9	<0.01
~70	50	6	12	72	25	34.72	8.04	<0.01
Total	377	41	10.88	520	116	22.31	19.78	<0.01

Table 4. Overall evaluation on rural middle-aged and elderly people with KOA in Fengxian District before and after drug treatment.

Group	Knee activity-related pain	15 m walking time (t/s)	Joint tenderness	ADL	Patient evaluation score
Loxoprofen					
Before treatment	9.4±2.1	41±12	1.9±0.8	6.8±1.5	8.4±2.2
After treatment	6.8±1.8	32±8	1.1±0.6	3.8±1.2	5.6±1.7
t test	$t=5.87; p<0.01$	$t=3.8971; p<0.05$	$t=4.996; p<0.01$	$t=9.753; p<0.01$	$t=6.2893; p<0.01$
Diacerein					
Before treatment	9.8±2.0	45±13	2.1±0.8	7.2±2.1	8.9±2.3
After treatment	7.8±1.8	37±8	1.8±0.5	5.4±1.8	6.8±1.9
t test	$t=4.6419; p<0.01$	$t=3.273; p<0.05$	$t=1.9859; p<0.05$	$t=4.0642; p<0.01$	$t=4.396; p<0.01$
Glucosamine					
Before treatment	9.2±2.4	39±15	2.0±0.8	5.7±1.2	8.5±2.8
After treatment	6.3±1.6	29±10	1.3±0.5	3.4±0.8	6.5±2.4
t test	$t=6.2787; p<0.01$	$t=3.4621; p<0.05$	$t=4.6338; p<0.05$	$t=9.9593; p<0.05$	$t=3.3868; p<0.01$

RESULTS

Situation of disease

The morbidity of middle-aged and elderly people in KOA in the group amounts to 17.50% while the morbidity of men and women are 10.88 and 22.31%. There are significance differences between men and women ($\chi^2 = 19.78, p<0.01$) (Table 3).

Comprehensive evaluation

Comparisons of knee activity-related pain, 15 m walking time (t/s), Activities of Daily Living and comprehensive evaluation for patients before and after intervention in loxoprofen, diacerein and glucosamine group showed significant differences ($p<0.05$) (Table 4).

Evaluation of efficacy

The overall response rates of each group are 90.20,

74.51 and 88.24%, respectively. Ridit analysis demonstrated that $R(-)_1 = 0.4424$, $R(-)_2 = 0.5825$ and $R(-)_3 = 0.4751$ by Ridit analysis. Considering $\chi^2 = 6.7253$, $p<0.05$, pointing out that the overall efficacy of the three groups of drugs were different, in which that of loxoprofen and glucosamine were better than that of Diacerein (Table 5).

Adverse reactions

The adverse reactions of loxoprofen are 1 patient with facial edema and gastrointestinal discomfort respectively, diacerein for 8 patients are gastrointestinal discomfort and glucosamine 1 patients with gastrointestinal discomfort and 1 patient with slight swirl. The significance of the difference among the three adverse drug reactions is $\chi^2 = 6.51, p<0.05$, among which the incidence of adverse reactions in diacerein group is higher.

DISCUSSION

KOA is a kind of common chronic diseases among

Table 5. Evaluation on efficacy of drug intervention for rural middle-aged and elderly people with KOA in Fengxian District.

Group	Remarkable progression	Progression	Improvement	Invalid	Response rate (%)
Loxoprofen	21	14	11	5	90.20
Diacerein	12	12	14	13	74.51
Glucosamine	17	17	11	6	88.24

middle-aged and elderly people, which are mainly found in women. Apart from mechanic wear, several factors, such as immunity, biochemistry and inheritance, are related to pathogeny. Pathological changes mainly take the form of cartilage degeneration and subchondral bone lesion, associated with change of synovium. The main clinical manifestations are morning stiffness, joint pain, swelling and dysfunction. Due to heavy load and mobility, knee joints turn out to be the part that KOA is most likely to occur and make the clinical treatment more difficult because of its complicated structure.

Pyramid Scheme for KOA treatment proposed by American college of Rheumatology in 1995 based on patients' education, exercise and reduction of weight, and was supplemented with external usage of NSAIDs when necessary, added up oral acetaminophen and nonsteroida anti-inflammatory agent in turns in case of invalid situations, injected with cortin in articular cavity in case of acute attack. In case of irreversible dysfunction, joint replacement can be conducted (Hochberg et al., 1995). Numerous scholars considered that drug treatment is of convenience, feasibility, reliable efficacy and easy maintenance. Drug treatment includes two types of drugs, which are for the improvement of symptoms and changing state of illness. Nonspecific NSAIDs belongs to drugs for symptom improvement, which fulfill the objective of anti-inflammation by suppressing COX enzyme activity. It can quickly solve or relieve patients' joint pain, tenderness, stiffness or hydrops and concomitant reversible limited joint movement, thus improving remarkably the patients' life quality. However, these drugs fail to change the natural progression of diseases and with higher incidence of adverse reactions in gastrointestinal tract.

In recent years, specific NSAIDs, for example, loxoprofen, has been widely applied in the treatment of KOA, demonstrating a better efficacy and tolerance (Geba, 2002; Cannon et al., 2000). In the present study, the overall response rate of loxoprofen group is 90.20% and the incidence of adverse reaction is 3.92%. According to reports at home and abroad, the overall response rate of loxoprofen in treatment of OA varies from 85.30 to 89.90% while the incidence of adverse reaction is 2.11 to 12.26% (Li et al., 2000; Waikakul and Waikakul, 1999), which is close to the data of the group. It suggested that loxoprofen, as a precursor specific NSAIDs drugs of new type of gastric nucosa with weak stimulation, had a quick effect on KOA, strong and balanced antiinflammation and slight gastrointestinal

stimulation. Therefore, loxoprofen can be one of the prosperous drugs for the treatment of KOA and listed as one of the major drugs for the treatment of KOA.

Diacerein is an important inhibitor for osteoarthritis IL-1. Some studies reported that it can lead to generation of cartilage and play a role of analgesia, ant-inflammation and abatement of fever *in vitro* and *vivo*. Meanwhile, it does not inhibit synthesis of prostaglandin due to its role in postponing the progression of diseases for osteoarthritis. A single blind, parallel study for 64 OA patients demonstrated that the role of diacerein in improvement of walking pain degree (VAS) and joint CGI grading was markedly better than that of placebo group and can relieve joint pain markedly as well as improving body function (Brahmachari et al., 2009). Moreover, it is of remarkable reconstruction function for joint structures and relieves the progression of pelvic OA patient's joint space stenosis (Dougados et al., 2001). The usage of diacerein in treatment of KOA turns out to be safe, effective and of long-term efficacy. Therefore, it became quite popular among KOA patients who fail to tolerate NSAIDs and acetaminophen and acted as optional drugs for treatment of KOA. However, it can also cause some complications like diarrhea (Bartels et al., 2010), which force part of patients to suspicious. There are significant differences ($p < 0.05$) among the aspect of knee activity-related pain, 15 m walking time (t/s), ability of daily living and comprehensive evaluation for patients, with a overall response rate reaching 74.51%; the incidence of adverse reactions amounts to 15.69%, which are all slight gastrointestinal discomfort. Long-term administration of diacerein can be tolerated by KOA patients.

By stimulating the biochemical synthesis and increasing uptake of calcareous skeleton, glucosamine increases the metabolism function and nutrition of cartilaginous tissue, improves and enhances viscosity of synovial fluid as well as providing lubrication function for joints so as to block the pathological process of KOA, prevent the progression of diseases, improve the joint activity function, relieve joint pain, inhibit and degrade the formation of joint degeneration. Assertive evidences that glucosamine serves as a kind of drug changing condition of KOA come from two recent reports: One is a clinical observation (Reginster et al., 2001) on 212 knee random, double-blinded control during 3-year course of treatment completed by Belgium, US, Italy and UK while the other is a double-blinded, random placebo control observation (Pavelka et al., 2002) on 202 KOA patients during 3-year course of treatment proposed by Czech and Italy. Both

reports demonstrated long-term treatment could prevent progression of KOA and thus considered to be the first drug to improve symptoms and change state of illness that conforms to modern classification. Some Chinese scholars who conducted 5-week random, double-blinded control observation on 108 KOA pointed out that the overall response rate in glucosamine sulfate group amounted to 82.27%. In the study, there are significant differences ($p < 0.05$) among the aspect of knee activity-related pain, 15 m walking time (t/s), ability of daily living and comprehensive evaluation for patients in glucosamine group before and after treatment, with a overall response rate reaching 88.24%; the incidence of adverse reactions amounts to 3.92%, which is close to that in the report at home and abroad. In recent years, the drug has been taken seriously by clinician and patients gradually. It is considered that we can master the opportunity and insist on long-term treatment of KOA, then the prognosis will be improved.

Conclusion

In the present work, we successfully demonstrated that drug intervention for treatment of KOA play a favorable role in improving symptoms, functions and enhancing the quality of life as well as postponing the progression of diseases. The adverse reaction of the above three kinds of drugs are all quite slight, though with differences. Loxoprofen, diacerein and glucosamine can be all listed as the first-line drugs for the treatment of KOA and drug intervention treatment in early stage shall be carried out initiatively for patients with indications and conditions. However, the efficacy of drug intervention for more severer KOA is quite limited. Therefore, the patients with a more severe KOA should be treated by other methods such as arthroscopic debridement or total knee arthroplasty (TKA).

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