Original Article

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The Effect of Colchicine in Improving the Symptoms of Patients with Knee Osteoarthritis

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ABSTRACT

BACKGROUND AND OBJECTIVE: Due to low effectiveness of drugs in osteoarthritis treatment, finding new drugs always consider. Although colchicine has been described as a disease moderator medicine for osteoarthritis disease or symptoms, few studies have been carried out about the effect of it in soothing symptoms of patients with knee osteoarthritis.

METHODS: This RCT was conducted on 62 patients with idiopathic knee osteoarthritis. Pain intensity, the degree of functional disability, and the patients' clinical health were assessed by VAS, modified WOMAC index and modified HAQ questionnaire, respectively. The patients were then randomly assigned to two groups of oral colchicine group (0.5mg/bid) and placebo group and undergone treatment for 4 months. Assessment repeated in 3rd and 4th months. IRCT code: IRCT2015071623240N1.

FINDINGS: Compared to the beginning of the study, the intensity of pain in both groups was reduced and the degree of functional disability and the patients' clinical health were improved in the 3rd and 4th months of study, too. Nevertheless, the percentages of pain severity improvement in colchicine group in comparison to placebo were significantly higher (3rd mo: 29% vs. 16%, respectively, p=0.030; 4th mo: 37% vs. 20%, respectively, p=0.014). In addition, the percentages of physical function improvement in colchicine group in comparison to placebo were significantly higher (3rd mo: 26% vs. 16%, respectively, p=0.048; 4th mo: 28% vs. 20%, respectively, p=0.036).

CONCLUSION: Use of colchicine for four months in patients with knee osteoarthritis can reduce pain and improve physical function.

KEY WORDS: *Knee Osteoarthritis, Colchicine, Placebo.*

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Introduction

Knee osteoarthritis causes serious morbidity especially functional disability in patients (1-4) and comes with a great cost to patients and healthcare systems (5, 6). It is estimated that with the aging of population in America, by 2020 the incidence of osteoarthritis increase 100-66% as well as the economic burden also increases (7). Symptomatic osteoarthritis of the knee is a common problem in approximately 12% of persons older than 60 years in the United States and 6% of all adults older than 30 years (8-10). Treatment goals include pain relief and minimize the loss of physical function. Drug therapy includes a wide variety of drugs and surgical treatment of the disease also occurs in severe cases (11).

Due to little effect of used drugs, finding new treatments is always interesting. Colchicine is known as moderator of the disease or symptoms, is an alkaloid having anti-inflammatory effects (12-15). So far in three study the effects of colchicine in combination with other conventional treatments have been studied on the symptoms of the disease (16-18), and that colchicine improved disease. Nevertheless, more evidence is needed to prove its effectiveness. Therefore, the aim of this study was to evaluate the efficacy of colchicine in symptoms modulation of patients with knee osteoarthritis.

Methods

This randomized double-blind clinical trial with registration number 1N20150716232401RCT: and after obtaining informed consent was done in 2011 on patients with knee osteoarthritis referred to Imam Hossein hospital in Tehran. 81 patients were enrolled based on inclusion criteria and were randomly assigned to two groups of colchicine (n=40) or placebo (n=41). But in the end, only 62 patients (32 patients in the colchicine group and 30 in placebo group) completed the study (Fig 1).

Patients aged 75-35 years with osteoarthritis based on the American College of Rheumatology criteria or ACR criteria and Kellgren & Lawrence radiographic criteria (19), the absence of CPPD-induced arthritis in other joints, lack of experience of gout and pseudo gout, absence of inflammatory diseases, liver diseases, kidney disease, cardiovascular disease, cardiomyopathy, neuropathy moderate to severe digestive problems (diarrhea, abdominal pain), fibromyalgia and infection, no history of knee replacement, avoiding the use of drugs with interaction with colchicine, the absence of any of the following tests: WBC<3500/mm3, HGB<10 mg/dl, Cr>1.3 mg/dl, Amino transfrase >45, .uric acid>6.5 mg/dl were enrolled. In addition, they must ensure that they had no intra-articular steroid use at least two months ago and the use of intra-articular hyaluronic acid for at least 3 months ago, the use of glucosamine, MSM or Chondroitin sulfate at least 4 to 6 months ago.

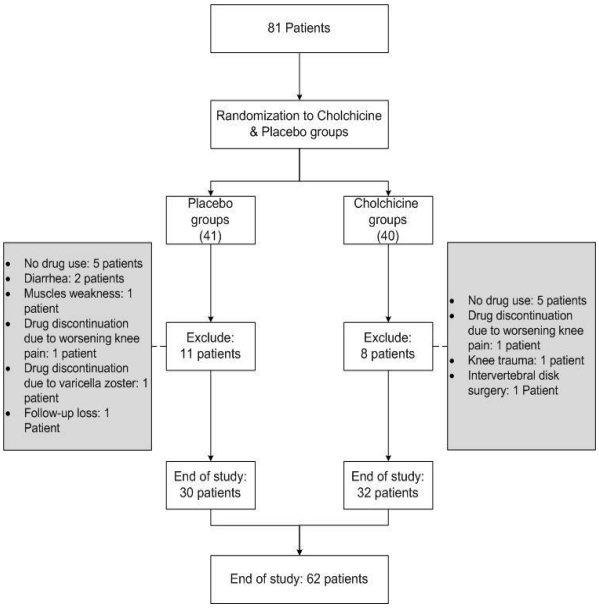

Figure 1. Algorithm of patients participating in the study

In addition, the absence of contraindications for use of colchicine, at least two clinical findings of inflammation (warmth, tenderness, effusion, and swelling of the tissues around the joint) in examination of the knee joint and cooperation in the study were also included in inclusion criteria.

Exclusion criteria of the study included not taking medications according to the study protocol or a change in dose, severe and intolerable side effects, intensification of unbearable knee pain, analgesic consumption during the treatment period for reasons other than pain, knee trauma or any problem interfering with osteoarthritis of the knee that prevents from use of drug and not visit for follow-up. Using a check list information were registered. Before starting the study and to justify the intensity of pain at baseline, the patients received full dose of naproxen (up to 1 g daily) for 2 weeks. Pain was evaluated based on the Visual Analog Scale or VAS, rate of functional disability based on modified Western Ontario and McMaster Universities Arthritis Indexes (modified

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WOMAC) and the clinical health based on modified Health Assessment Questionnaire (modified HAQ) .VAS scale is a 10 cm line (0: no pain; 10: maximum pain), and the patient is asked to point out the line that reflects the intensity of his/her pain.

Because of repeated measurements of each patient, VAS could very well represent a change in the patient's pain (20). Modified WOMAC index is adjusted form of WOMAC index for eastern communities evaluating the status of patients with osteoarthritis of the knee and hip (21, 22).

This index with 27 questions measures three aspects of pain, stiffness and physical performance and has three scales and a total score (0-108) that the higher score indicates the worse symptoms. Modified HAQ questionnaire assessed the physical function in patients (23), and is approved for use in osteoarthritis (24). This questionnaire contains 8 questions about daily activities (activities related to the upper and lower limbs that each of them have 4 questions). Each question has four answers from doing without difficulty (score 1) to inability to work (score 4).

Total score reflects the patient's inability to doing work. A higher score means more disability. In our study, only four questions related to the lower limbs were asked. Thus, the questionnaire score was between 4 and 16. Patients were randomly assigned to two groups of oral colchicine (5/0 mg / bid) and placebo. Colchicine and placebo were made in Modava pharmaceutical company. To study be double-blind, necessary amount for the consumption for a period of 4 months, each drug was poured into a similar drug envelope and a number was installed on the envelope that the doctor and patient were blinded which patients belongs to determined groups to the end of study. Placebo tablets with a similar appearance to colchicine containing starch was prepared in the Laboratory. Patients taking pills twice a day, and the patients were asked not to make a change in the type and dose of your previous medicine.

During the study the patients were followed by phone for use of drugs and their side effects. In the third and fourth month of treatment, the patients were asked again to complete questionnaires. Data analysis was performed using statistical software 13 SPSS. Statistical tests including chi-square test, independent t-test, Mann-Whitney U test and repeated measure ANOVA test were used.

Percentage of improvement in scores for the questionnaires or subscales were calculated as follows; the result of subtracting the baseline score from the score in the third and fourth month of the beginning of the study were divided and multiplied by 100. $p<0.05$ was considered significant.

Results

61 patients (98%) were female and the average age of the patients was 58±9 years. Significant differences between two groups was observed based on demographic and clinical characteristics of patients (table 1).

Table 1. Comparison of patient characteristics at baseline

Group Variable	Colchicine (n=32) N(%)	Placebo (n=30) N(%)	P-value
Demographic Characteristics			
Age (year) Mean±SD	8±57	10±59	0.325*
Length (cm) Mean±SD	6±175	6±156	0.746*
Weight (kg) Mean±SD	13±79	13±78	0.961*
BMI :Mean±SD	5±32	۳۲±۵	0.717*
Characteristics of knee osteoarthritis			
Disease duration 5≥	21(66)	13(43)	0.078**
>5	11(34)	17(57)	
Bilateral osteoarthritis	26(81)	29(97)	0.055**
Morning stiffness ، Minute :Median) Inter-quartile range(	5(0-20)	3(0.155)	0.535***
Knee physical examination			
Effusion	19(59)	13(43)	0.207**
Tenderness	32(100)	27(90)	0.067**
swelling	10(31)	10(33)	0.861**
anterior and posterior cruciate ligaments injury (ACL and PCL)	0(0)	0(0)	–
Locking of Knee	12(38)	10(33)	0.732**
Giving way	12(38)	11(37)	0.946**
Radiographic findings of knee			
Osteophytes	12(38)	16(53)	0.211**
marginal sclerosis	29(91)	23(77)	0.135**
The joint space loss	24(75)	20(67)	0.470**
Lab data			
Creatinine mg.dL	0.98±0.6	0.95±0.2	0.844*

* Independent t test, ** chi-square test, Mann-Whitney U test ***

Table 2. Comparison of functional disability scores based on modified WOMAC index at baseline

Group	Colchicine	placebo	P-value*
Pain intensity	11±5	10±4	0.036
Stiffness	5±2	4±2	0.065
Physical function	45±12	42±10	0.370
Inability of general performance	71±19	67±17	0.424

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At baseline, no significant difference between the two groups in terms of pain intensity (colchicine group: 4.2±1.8, placebo: 3.2±1.7, p=0.094), or functional disability scales or their total score (table 2) and health assessment score (colchicine group: 2±9, placebo: 3±9, p=0.617) was found. Pain intensity decreased from baseline until the end of the study in both groups (p<0.001). However in colchicine group the pain intensity was significantly lower in the fourth month than the third month, while in the placebo group difference was not significant between the fourth and third month.

Measures of functional disability and health evaluation score in both the third and fourth months compared to baseline were significantly reduced. However in the placebo group, pain intensity, functional disability scale, only in the third month was significantly reduced compared to baseline (table 3).

Table 3. Comparison of outcomes of the study (pain, functional disability and health assessment) during the study

Group		Baseline Mean±SD	Third month Mean±SD	Fourth month Mean±SD	P-value*
Pain intensity based on VAS scale	Colchicine group	8.1±2.4	5.9±2.7	5.1±2.6	**<0.001
	Placebo group	7.1±2.3	5.9±2.5	5.5±2.5	***<0.001
Functional disability scores based on the modified WOMAC index					
Pain intensity	Colchicine group	11±5	7±4	7±6	***<0.001
	Placebo group	10±4	7±4	8±6	****0.012
Stiffness	Colchicine group	5±2	3±2	3±2	***<0.001
	Placebo group	4±2	3±2	3±3	***0.011
Physical function	Colchicine group	45±12	34±14	33±18	***<0.001
	Placebo group	42±10	35±10	37±15	***0.002
Inability of general performance	Colchicine group	71±19	53±21	53±28	***<0.001
	Placebo group	67±16	56±15	58±23	***0.002
Health Assessment Questionnaire score based on modified HAQ	Colchicine group	9±2	7±2	6±2	***<0.001
	Placebo group	9±3	7±2	7±2	***<0.001

*Repeated measures ANOVA test, ** significant improvement in the third and fourth months compared to baseline and also third month compared to the fourth month, *** significant improvement in the third and fourth months compared to baseline, **** significant improvement in the third month compared to baseline.

Table 4. Comparison of improving the outcomes of study (pain, functional disability and health assessment)

Variable	Group	Colchicine group	Placebo group	P-value*
Improvement of pain intensity compared to baseline according to VAS scale				
	Third month	29±24%	16±28%	0.030
	Fourth month	37±27%	20±31%	0.014
Improvement of functional disability scores based on the modified WOMAC index compared to baseline.				
Pain intensity	Third month	34±30%	26±31%	0.256
	Fourth month	35±47%	15±53%	0.162
Stiffness	Third month	32±33%	22±41%	0.272
	Fourth month	35±41%	26±46%	0.377
Physical function	Third month	26±21%	16±20%	0.048
	Fourth month	28±31%	12±30%	0.036
Inability of general performance	Third month	26±22%	16±20%	0.074
	Fourth month	27±31%	12±30%	0.066
Health Assessment Questionnaire score based on modified HAQ compared to baseline				
	Third month	20±19%	15±22%	0.648
	Fourth month	26±23%	16±20%	0.159

* Mann-Whitney U test

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Improvement in pain intensity and physical function scale from functional disability in the third and fourth months compared to baseline in the colchicine group was significantly higher than the placebo group ($p<0.05$). While the percentage of improvement in other measures of functional disability and health evaluation score in the third and fourth percent improvement compared to baseline were not significantly different between the two groups. At the end of treatment, 34 patients (55%) had decreased joint tenderness. Improved effusion in 17 patients (27%) and improved meniscal injury (improved locking of the knee and draining the knee (Giving way) in 7 patients (11%) was observed. Only improved tenderness in the colchicine group was significantly more than the placebo group (respectively 70% and 40%, $p=0.023$). Improved effusion (respectively 38% and 17%, $p=0.066$) and improved meniscal injury (6% and 17%, $p=0.195$) in the colchicine and placebo groups showed no significant difference. Uric acid in the blood of patients in the treatment group was significantly lower compared to the placebo group (respectively 4.1±0.8 mg/dL and 5.9±1.4 mg/dL, $p=0.001$). In patients who completed the study there was not certain side effects.

Discussion

The study showed that the use of colchicine or placebo for four months in patients with osteoarthritis of the knee (without chondrocalcinose) reduced patients' pain that in the colchicine group stays longer. The percentage of improvement in pain intensity and physical functioning scale in the third and fourth months was higher in the colchicine group. Physical examination revealed that tenderness considerably improved with taking colchicine. Das and colleagues in a study of 39 patients with osteoarthritis of the knee in both colchicine and placebo group were treated for 5 months reported that colchicine group was better than the placebo group in the severity of knee pain and functional disability scores at weeks 16 and 20 and the proportion of patients who had a 30% or better treatment response at week 16 was greater in the colchicine group. The effects of colchicine treatment at week 20 was still intact. In that study, 30% of patients had definite criteria for chondrocalcinose (CPPD) (16). Das and colleagues in another study investigated the effect of adding colchicine drug to nimesulide in 36 patients with osteoarthritis of the knee (8 patients with primary crystals of CPPD) for 5 months and reported that the improvement rate of 30% in colchicine group was significantly higher than the placebo group at 20th week of treatment (17).

Aran and colleagues also investigated the effects of colchicine on modulation of symptoms in 61 postmenopausal women with primary osteoarthritis without radiographic evidence of atypical osteoarthritis or chondrocalcinose for 3 months and reported that the use of acetaminophen was significantly lower in the colchicine group than in the placebo group. In addition, at the end of the study, the amount of improvement in patient, physician global assessment and pain intensity scale were significantly higher in the colchicine group (18).

Our study showed that the use of colchicine for 4 months in patients with osteoarthritis of the knee can be effective in improving pain and physical function in patients. The drug was well tolerated and side effects were not seen. What distinguishes this study from previous studies conducted by Das et al (16,17) regarding the impact of colchicine in patients with osteoarthritis of the fact is in our study CPPD patients were not enrolled. One of the factors that can cause inflammation in the knee osteoarthritis is CPPD. Anti-inflammatory effects of colchicine by interfering with the structure and function of microtubules that is essential for inflammatory activity of phagocytes (12) and inhibits the secretion of inflammatory cytokines and formation of eicosanoids due to inhibition of phospholipase A2 in monocytes and neutrophils (13, 14). By blocking some of the enzymes involved in inflammation may also have anti-inflammatory effects (15). On the other hand currently there is no acceptable standards for inflammation in osteoarthritis.

The presence of two or more of the symptoms of inflammation, such as warmth, effusion, soft tissue swelling and tenderness of the joint border as characteristic symptoms of inflammation are considered. While our study showed that colchicine may be beneficial in improving pain and physical performance of osteoarthritis patients without the CPPD. In this respect, our results are consistent with study of Aran and colleagues conducted in patients with osteoarthritis without CPPD (18).

In study of Aran and colleagues intervention period was 3 months and was conducted in women after menopause. While in our study the intervention period was 4 months and involved patients were not limited to women in menopause. Given that current treatments

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for osteoarthritis are all symptomatic, and therapies that can change the disease condition (disease modifying) or removing pathological condition in osteoarthritis has not been found, it may be possible to use colchicine for this purpose. Used dose in our study and three additional studies was 5.0 mg twice a day), it seems that only can prevent the inflammation not the treatment of inflammation.

Hence, the use of conventional drugs such as intra-articular corticosteroids to treat inflammation is necessary. Although the results of our study and three additional studies also demonstrated the effects of colchicine in improving pain and function in osteoarthritis patients, it should be noted that in all of these studies the duration of intervention was short and long-term studies are required to determine the exact drug dose, duration of treatment, side effects and mechanisms of action.

The findings of this study showed that the use of colchicine was associated with greater percentage of improvement in pain severity, physical function and the tenderness. Thus, it seems that colchicine in patients with osteoarthritis pain and to improve physical function can be used.

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