ORIGINAL ARTICLES

The slow-acting, symptom modifying effects of colchicine in primary knee osteoarthritis

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Abstract

Aim: To determine whether the therapeutic use of colchicine along with etodolac (selective cox-2 inhibitor NSAIDs) confer any beneficial effect in the treatment of osteoarthritis of knee joint.

Materials and methods: Forty selected subjects were randomized to receive either 0.5 mg of colchicine twice daily or placebo for 26 weeks.

Results: Visual analog scale (VAS), Western Ontario and McMaster University Osteoarthritis total scale (WOMAC), and patient global assessment and physician global assessment scores were recorded on day 0, weeks 2, 6, 10, 14, 18, 22 and 26. Improvement rate at the end of 22 week was higher in colchicine group than placebo, as measured by VAS score (46.88 vs.51.11;P=0.033), WOMAC score (18.88 vs.24.56; P=0.019), patient global assessment score(34.69 vs. 38.33; P=0.039) and physician global assessment score (20.00 vs. 26.39; P=0.02).

Conclusion: Subjects receiving colchicine plus etodolac exhibited significantly better symptom control at the end of 22 weeks than the placebo group.

Introduction

Osteoarthritis (OA) is the third most common diagnosis made by general practitioners in elderly patients and the most common arthropathy to affect knees. OA, a degenerative disease, is defined as a conglomeration of small and large injuries to the joints followed by ineffective cartilage repair.[1] Risk factors for knee OA include ageing, female gender, being overweight, prior knee injury and a positive family history.[2, 3, 4, 5, 6] About 25% of adults over 55 years of age experience significant knee pain and half of them have radiographic changes of OA and a quarter have significant disability. Role of inflammation in OA is controversial, but it may be crucial to OA pathogenesis, as synovial inflammation is frequently observed. Articular calcium deposition, comprising of calcium phosphate dehydrate (CPPD) and basic calcium phosphate crystals (BCP), is seen in majority of joints affected by severe OA. The inflammatory potential of CPPD crystal is similar to monosodium urate crystals. Inflammatory mediators, released from cartilage into the synovial space, activate synovial cells to produce chemoattractants and initiate inflammatory response. Colchicine, an alkaloid commonly used for the treatment of gout, aids in preventing crystal-induced inflammation. Certain literature findings suggest that colchicine may be beneficial in improving the symptoms of OA. A randomized, double-blind, placebo-controlled trial by Das *et al.* showed greater symptomatic relief at 20 weeks when colchicine was added to nimesulide in 36 patients with knee OA.[7] The present study determined whether addition of colchicine to etodolac (selective cox-2 inhibitor NSAIDs) may confer any beneficial effect on osteoarthritis of knee joints.

Materials and methods

Patients of both gender, between 40 and 70 years of age, fulfilling the diagnostic criteria of American college of rheumatology (ACR) for OA of knees, were considered for the study. The inclusion criteria considered were occurrence of moderately severe symptomatic OA, determined by Western Ontario and McMaster University Osteoarthritis total scale (WOMAC) score ≥25, and subjects without clinical or radiological evidence of

other rheumatological, immunological illnesses, renal, hepatic diseases, allergies or contraindication to the use of etodolac, tramadol, or colchicine. The WOMAC score was recorded after receiving oral etodolac for 2 weeks at a dose of 400 mg twice daily. The score was recorded on Likert scale of 0-4, where 0=no pain/limitation; 1=mild pain/ limitation; 2=moderate pain/limitation; 3=severe pain/ limitation; and 4=very severe pain/limitation. The total score was the sum of all responses. The exclusion criteria considered were: positive rheumatoid factor (RF), positive C-reactive protein (CRP), serum uric acid >6.0 mg/dl, total leukocytes counts <4000/mm, serum creatinine >1.3 mg/dl, serum transaminases >45 units/liter, uncontrolled diabetes, congestive heart failure, neuropathy, history of bleeding peptic ulcer, major knee surgery at knee joints, and having signs of inflammation in elbow, wrist, shoulder and first MTP joint.

Informed consent was obtained for all the study participants. Clinical assessment and thorough examination were conducted on day 0 and at weeks 2, 6, 10, 14, 22 and 26 for all the patients. Clinical assessment consisted of physical examination and primary and secondary measures of diseases assessment. The patients underwent the following investigations at baseline and after 22 weeks: hemoglobin (Hb), total leukocyte count (TLC), differential leukocyte count (DLC), erythrocyte sedimentation rate (ESR), serum creatinine, serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), blood sugar (fasting and post prandial), serum uric acid, rheumatoid factor, and c-reactive protein. X-ray of the knee joint (anteroposterior and lateral views in standing position) was taken only at the beginning of the study. Patients were randomized to receive either 0.5 mg of colchicine twice daily or placebo. They were randomized in blocks of four by a person who was not involved in the trial and the randomized codes were not decoded till the end of the study. All the subjects received etodolac for initial 14 days and the trial was begun on the 15th day. All the patients received etodolac (400 mg/BD) throughout the study and tramadol (50 mg) as rescue drug. The study group received the investigational drug in the form of tablets and the placebo group received identical tablets constituted by starch. The subjects were not allowed to receive other NSAIDS or corticosteroids during the trial. The assessments conducted at 6, 10, 14, 18, 22 and 26 weeks of follow-up included: clinical assessments, visual analog scale (VAS) score of knee pain, WOMAC score, and patient global assessment and physician global assessment scores. The commonly reported adverse events were abdominal pain and loose stool, and the newly reported adverse events were recorded in an open format.

The primary measure of clinical response was 30% improvement in total WOMAC scores and VAS from baseline at 22 weeks. The other efficacy end points were patient global assessment and physician global assessment scores. Total number of etodolac and tramadol received was also recorded. The VAS score was documented on 15 cm scale. An intergroup univariate analysis by student's t-test was performed between the assessment variables at 12 and 22 weeks in both the groups.

Results

The study population (n=40) consisted predominantly of females (65%) with mean age of 51.8 years and mean

Table 1: Comparison of the outcome measures between the colchicine and control groups

Variables	Baseline			10th week			20th week			26th week		
	Colchicine	Control	P	Colchicine	Control	P	Colchicine	Control	P	Colchicine	Control	P
WOMAC score	41.94	42.11	0.96	26.44	31.89	0.14	18.88	24.56	0.019	17.13	22.11	0.011
VAS score	80.63	77.5	0.33	46.88	40.63	0.76	45.56	51.11	0.033	40.63	45.56	0.015
Patient global assessment score	56.56	59.72	0.56	46.25	45	0.79	34.69	38.33	0.039	32.81	35.28	0.047
Physician global assessment score	40.63	40.56	0.98	6.33	7.25	0.81	20	26.39	0.02	15.63	24.44	0.00009

Abbreviations: WOMAC = Western Ontario and McMaster University Osteoarthritis Index; VAS =visual analog scale

duration of disease of 6.5 years (8 months to 10 years). On decoding the randomized list, 20 patients had been assigned to the colchicine group and 20 patients to the placebo group. Of the 20 patients assigned to the colchicine group, 16 patients completed 6 months of the study; Out of the 4 patients, 3 patients left the study after 10 weeks due to improvement in symptoms and 1 patient by 14th week due to unknown reason. Of the 20 placebo subjects, 18 completed 6 months of study and 2 were lost to follow-up. The 30% responder rate at 22 weeks was significantly higher in colchicine + etodolac group than placebo + etodolac group in total WOMAC score (P=0.019). The VAS scores (mean±SD) noted in the colchicine and placebo groups were 46.88±14.93 and 51.11±10.20 respectively (P=0.033). The patient global assessment scores noted in the colchicine and placebo groups were 34.69±12.58 and 38.33±12.01 respectively (P=0.039). The corresponding physician global assessment scores in colchicine and placebo groups were 20.00±8.94 and 26.39± 7.23 (P=0.02) (Table 1).

Discussion

The present study recruited only those patients who fulfilled the diagnostic ACR criteria for OA and having involvement of bilateral knee joints. The patients who had atypical joint presentations for primary OA were excluded. The addition of colchicine to etodolac showed significant improvement in pain scale after 22 weeks. Although comorbid conditions like fibromyalgia may interfere the VAS scale evaluation, none of the recruited subjects had fibromyalgia at the time of the study. The changes in VAS scale were better and statistically significant in colchicine treated group. The requirement of tramadol in the colchicine group (3 out of 16) was lesser when compared to the placebo group (6 out of 18).

Colchicine at trial dose (0.5mg twice a day) was well tolerated and there was no significant increase in newly reported adverse events compared to the placebo group. Some patients complained of symptoms suggestive of acid peptic disease. This side effect could be due to etodolac use and not because of colchicine as these patients responded well to proton pump inhibitors.

Several studies have evaluated the efficacy of colchicine addition to the routine treatment regimen of OA. One such randomized controlled trial was conducted on 39 patients with OA of the knee and persisting inflammation. In addition to 2 weeks of piroxicam treatment and intraarticular steroid injection, the subjects were randomly assigned to receive colchicine 0.5 mg twice daily. The subjects who received colchicine demonstrated significantly greater symptomatic benefit at 16 and 20 weeks than the intraarticular steroid and piroxicam alone group.[7]

Another randomized double-blind placebo-controlled trial showed significantly better symptom-modifying effects when colchicine was added to nimesulide over a 5-month period in OA patients, irrespective of the occurrence of CPPD crystals.[8] In the present study, patients without inflammation at baseline were benefited by colchicine and the results were consistent with the aforementioned study findings.

CPPD crystal deposition is very common in primary OA. Studies on synovial fluid have demonstrated that the deposition of calcium crystals occur in 30-60% of unselected OA patients.[9, 10] The precise mechanism of CPPD crystal deposition is not known, but their formation is affected by altered levels of ATP, inorganic pyrophosphates and phopshates, as well as changes in the cellular matrix.[11, 12] The role of crystals in worsening the symptoms OA is underrated at present. Cooke has showed that 60% of joints affected by OA had evidence of synovial inflammation at the time of joint replacement. In addition, studies have reported that the synovial lymphocytic infiltrate correlates with interleukin 1β levels in synovial fluid and MMP-1 expression.[13, 14] Toll-like receptors (TLRs) and nod-like receptors (NLRs) have been implicated in the inflammatory effects of CPPD crystal. TLRs may directly or indirectly activate matrix metalloproteinase, thereby directly contributing to cartilage degradation.[15, 16]

In chronic and pseudo gouts, the use of colchicine has been advocated for the prevention of recurrent acute flares. The acute effect of colchicine in pseudo gout is not as impressive as those in acute gout. Interestingly, colchicine has been shown to inhibit elastase, a matrix metalloproteinase (MMP), in patient with chronic obstructive pulmonary disease, thereby preventing the progression of emphysema in patient who had stopped smoking.[17] Considering the pivotal role of MMPS in the degenerative process of OA, the action of colchicine on various MMPs could be attributed as a predominant mechanism responsible for the disease modifying action of the drug.[18]

In conclusion, colchicine, having good safety profile

for long-term use, could be a potential and affordable treatment for relieving the symptoms of OA and preventing further progression.

Competing interests

The authors declare that they have no competing interests.

Citation

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