A double-blind randomised controlled trial appraising the symptom-modifying effects of colchicine on osteoarthritis of the knee

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Abstract

Objective
Osteoarthritis (OA) is the most common articular disease. Common OA treatments are either not effective or associated with side effects. Calcium-containing crystals are quite common in primary OA and they worsen or may cause OA through induction of inflammation by neutrophils. Colchicine inhibits urate-crystal and calcium-pyrophosphate (CPP) crystal induced inflammation and elastase, a matrix-metalloproteinase (MMP) that play a pivotal role in degenerative joint processes. Hence, it was hypothesized that it may have symptom-modifying effects on OA.

Methods
Sixty-one postmenopausal patients with primary knee OA were enrolled. None of them had joint involvement atypical for OA or evidences of chondrocalcinosis in radiographic studies suggesting the presence of calcium-pyrophosphate-deposition-disease (CPPD). Participants were allocated to two groups receiving 0.5mg colchicines BID or placebo. Both groups received common OA treatments. Acetaminophen less than 2gr/day was used as rescue-analgesic. The efficacy end points were: patients' global assessment and physician's global assessment, recorded on a VAS (visual analogue scale). Statistical analysis was performed 3 months later.

Results
Thirty-one patients were assigned to the colchicine group. Fifty-eight patients were present for the last survey. Only 1 patient in colchicine group encountered adverse effect of colchicine without significant difference between the two groups. Acetaminophen consumption was significantly less in the colchicine (879.3±369.7) compared to placebo group (1620.7±393.1, p=0.000). Improvement rate at the end of 3 months was significantly higher in the colchicine group for both patients' global assessment and physician's global assessment measures compared to placebo group, (11.14±4.06 vs. 3.14±2.18, p=0.000) and (9.83±3.799 vs. 3.72±3.35, p=0.000), respectively.

Conclusion
The efficacy and safety of colchicine for pain reduction in OA was affirmed by our double-blind randomised controlled trial.

Key words
colchicine, knee osteoarthritis, visual analogue scale

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Introduction

Osteoarthritis (OA) is the most common articular disease characterised by the breakdown of articular cartilage. The pain in OA is due to articular and periarticular elements other than the cartilage (1). Traditionally it was considered to be a non-inflammatory disease however today the acute flares are accepted as a component in the course of the advanced and erosive OA (2). There is wide support that calcium crystals worsen or may cause OA and vice versa.

Monosodium urate, calcium pyrophosphate dihydrate, or basic calcium phosphate crystals can be the cause of inflammation via neutriphiles, by induction of protease synthesis and secretion and arachidonic acid metabolism by synoviocytes and macrophages. This redounds in bone and articular damage as well as degenerative joint disease. Calcium-containing crystals are quite common in primary OA, existing in a majority of patients due to different studies. Moreover the crystal arthropathy is seen with OA. Hence, it can be said that crystal presence may have pertinence in the symptom genesis in OA (3-7).

The effectiveness of colchicine has been shown previously in preventing calcium crystal induced inflammation. The inflammation is attenuated in these patients by colchicine through phosphorilation of thyrosin created by microcrystals. Moreover, colchicine inhibits elastase a matrix metalloproteinase (MMP) in chronic obstructive pulmonary disease (COPD) patients (8). Thus, it is hypothesized that colchicine could improve the symptoms and modify the disease in patients with OA (9-11).

We conducted this study on OA patients regardless of the presence of clinical signs of inflammation to evaluate the advantages and feasibility of addition of colchicines in comparison to the adjunction of placebo to common OA treatments, in our randomised double-blind placebo-controlled trial.

Material and methods

Sixty-one postmenopausal women between 49 and 78 years of age with the diagnosis of primary OA, based upon the American College of Rheumatology Criteria (ACR) were enrolled in our study. Patients were included if they fulfilled ACR criteria inclusive: knee pain and; at least three of the following 6 criteria: 38 years of age or older, stiffness lasting less than 30 minutes, crepitus, bone tenderness, bone enlargement and no warmth to the touch, likewise the presence of joint space narrowing, subchondral bone cyst, subchondral sclerosis and osteophyte in their radiographic studies, plus the following laboratory findings suggestive of OA (12-13). All participants had moderate-to-severe knee osteoarthritis determined by a score of 20 to 29 measured by Oxford Knee Score, *i.e.* 12-question questionnaire assessing patients with knee OA during the past 4 weeks. The scores are categorised into 4 categories of 0 to 19 indicating severe knee arthritis and a high probability that the patient may well require some form of surgical intervention; 20 to 29 indicating moderate-to-severe knee arthritis; 30 to 39 showing mild-to-moderate knee arthritis; 40 to 48 for cases with satisfactory joint function.

The exclusion criteria were the presence of any clinical or radiologic evidence of rheumatoid arthritis (RA) as well as other immunologic diseases, GI upset, renal or hepatic diseases, history of allergy, intraarticular injections in the past 3 months or any contraindications to the use of colchicines. None of the patients had joint involvement atypical for OA (the elbow, wrist, shoulder, and MCP joints) or any evidence of chondrocalcinosis in their radiographic studies suggesting the presence of calcium pyrophosphate deposition disease (CPPD). All patients had a negative rheumatoid factor, Hb>10 mg/dl, total leukocyte count >4000/mm^3, serum creatinine <1.2 mg/dl, transaminases <40 units/litre and normal ESR or CRP. Uric acid was also checked for all patients and the values over 6.5 mg/dl were considered abnormal.

All participants were given written informed consent to take part in the study. Patient information was saved in the hospital data base and only the investigators had access to it. Neither the patients nor investigators were informed of the treatment assignment for

each patient making this a double blind study. Our Institutional Review Board (Ethics Committee of the university) approved this study. Colchicine is an FDA approved drug and since both groups were receiving common OA treatment in addition to study drugs, patients in placebo group were also taking necessary treatment.

Patients were randomised and allocated to two groups, receiving either 0.5 mg of colchicine twice daily or placebo plus common OA treatments, inclusive (indomethacin 25 mg BD/TDS, diclofenac 50 mg BD/TDS and physiotherapy) which were continued if required by patients. Clinical assessment was performed on screening date and 3 months later and consisted of subjective (patients' global assessment) and physical examination (physician's global assessment) measures (Fig. 1). An orthopaedic surgeon performed all the clinical assessments. Biochemical evaluation and urinalysis were performed as baseline. Standard erect anteroposterior and lateral radiographs were taken and assessed independently by the orthopaedic surgeon. Randomisation was executed with the balanced block method by a person not involved in the study. Concomitant therapy with corticosteroids was not permitted. Acetaminophen less than 2000mg/day was used as rescue analgesic. Patients were advised not to use any analgesic on the day of visit. The study drug was provided in bottles and consisted of white tablets containing 1 mg colchicine. The placebo was supplied as identical tablets containing vitamin B6 in a much lower dosage than the safe upper limit of vitamin B6 dose for daily consumption (14).

The efficacy end points were: The patients' global assessment of the severity of disease, and physician's physical findings. All the end points were recorded on a VAS (visual analogue scale). All VAS scores were recorded on a 15-cm scale, considering the range of 0–4.9 as poor, 5–9.9 as good and 10–15 as excellent). In patients who had equal involvement of both knees, the right knee was considered as the index. Statistical analysis was performed by *t*-test and chi-square after a 3-month period, using SPSS software (version 11.5; SAS,
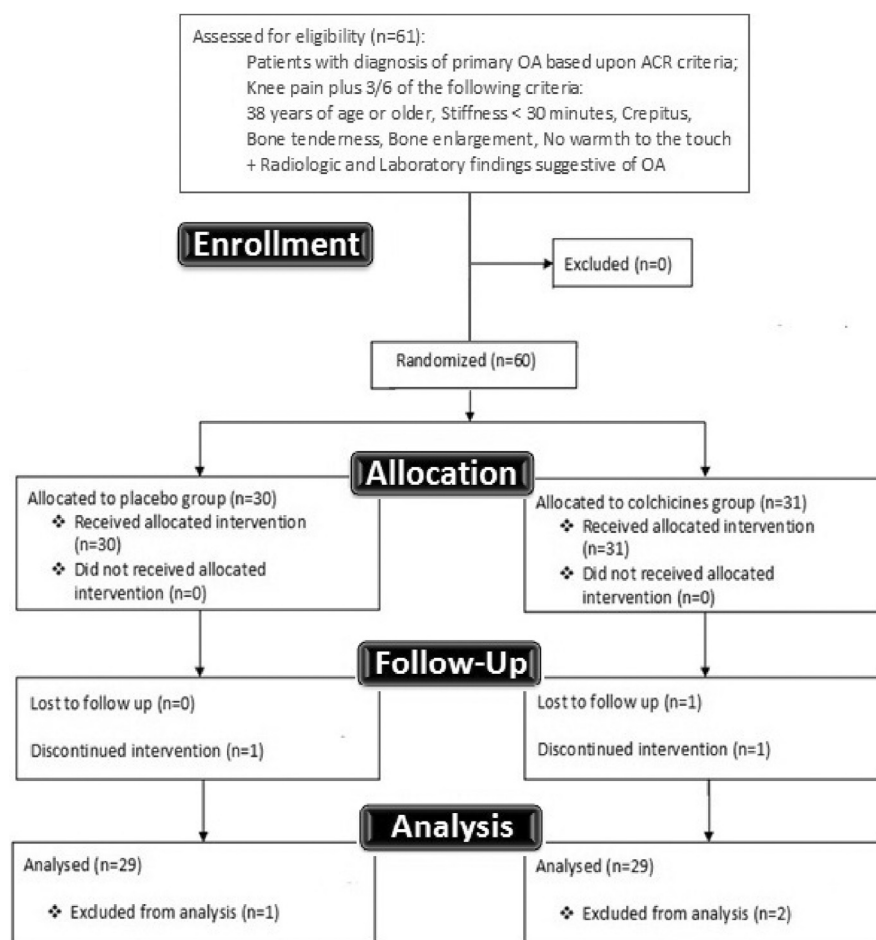

Fig. 1. Flow-chart.

Chicago, IL). *P*-values ≤0.05 was considered statistically significant.

Results

Sixty-one patients were enrolled with a mean age of 60.15 years (ranging from 49 to 78 years), distributed into two groups of colchicine (60.225±7.81 years) and control (60.07±7.89 year). The mean duration of the disease amongst study population was 6.3 years (ranging from 1 to 21 year). Thirty-one and 30 patients were assigned to the colchicine and control group, respectively. There was no statistically significant difference among the study groups regarding their mean age, the abnormal uric acid level, mean uric acid level, night pain and joint effusion, as well as Oxford knee score for diagnosis of the severity of knee OA and the number of patients receiving different common OA treatments. Conclusively, baseline demographic data, clinical and physical findings and biochemical measures were well matched between the 2 groups, showing that our randomisation was precisely performed (Table I).

Fifty-eight out of the total group were present for the final visit. Amongst the 31 patients assigned to the colchicine group, 29 completed 3 months of follow-up; one was lost to follow-up and 1 withdrew due to drug-related nausea, vomiting and diarrhoea. One patient from the placebo group also withdrew due to lack of treatment efficacy and satisfaction. There were no differences between the number of patients who withdrew from both groups. The data of the withdrawn patients was not considered in the final analysis. There was only 1 patient in the colchicine group who encountered the adverse effect of nausea, vomiting and diarrhoea whilst, no adverse effect was reported from the placebo group and the difference was not significant.

The patients' global assessment and physician's global assessment were sig-

Table I. Characteristics of patients.

	Colchicine	Placebo	p-value
Mean age	60.23 (7.81)*	60.07 (7.89)*	0.937
Oxford Knee Score	25.10 (3.39)*	25.41 (2.98)*	0.249
Mean uric acid level	6.20 (1.70)*	5.79 (1.78)*	0.368
Uric acid level	19 (61.29%)	21 (70%)	0.328
Night pain	24 (77.41%)	21 (70%)	0.357
Joint effusion	9 (29%)	12 (40%)	0.264
Distribution of patients on common OA treatment during follow-up			
Indomethacin 25 mg BD/TDS	17 (13.7%)	19 (15.3%)	0.126
Diclophenac 50 mg BD/TDS	14 (11.3%)	15 (12.1%)	0.143
Both indomethacin and diclophenac	3 (2.4%)	5 (4%)	1.000
Physiotherapy	18 (14.5%)	16 (12.9%)	1.000

Values are number of patients (percentage); *Values are the mean (±SD).

Table II. Outcome measures: comparison between the colchicine and control groups.

	Colchicine (95% CI)	Placebo (95% CI)	p-value
Patients' global assessment	11.14 ± 4.068 (9.59-12.69)	3.14 ± 2.183 (2.31-3.97)	0.000
Physician's global assessment	9.83 ± 3.799 (8.38-11.27)	3.72 ± 3.358 (2.45-5.00)	0.000
Acetaminophen consumption (number)	1.76 ± 0.739* (1.48-2.04)	3.24 ± 1.431* (2.94-3.54)	0.000
Acetaminophen consumption (mg/day)	879.3 ± 369.7** (738.6-1019-9)	1620.7 ± 393.1** (1471.1-1770.2)	0.000

Values are the mean ± Standard deviation (SD); The units are based on cm; *The values are number of acetaminophen tab/day; **mean acetaminophen consumption (mg/day).

Table III. Distribution of the results.

		Poor	Good	Excellent	Total
Patients' global assessment	Colchicine	2 (6.9%)	6 (20.7%)	21 (72.4%)	29 (100.0%)
	Placebo	25 (86.2%)	4 (13.8%)	0 (0.0%)	29 (100.0%)
	Total	27 (46.6%)	10 (17.2%)	21 (36.2%)	58 (100.0%)
Physician's global assessment	Colchicine	4 (13.8%)	5 (17.2%)	20 (68.9%)	29 (100.0%)
	Placebo	22 (75.9%)	5 (17.2%)	2 (6.9%)	29 (100.0%)
	Total	26 (89.7%)	10 (34.4%)	22 (75.8%)	58 (100.0%)

Values are number of patients (percentage).

nificantly higher in colchicine compared to placebo group in VAS index of knee pain at the end of the 3-month follow-up. Moreover, the mean acetaminophen consumption (mg/day) was significantly lower in colchicine group than placebo group (Table II). The distribution of the results of patients' global assessment and physician's global assessment are depicted in Table III and Figs. 2 and 3.

Discussion

Osteoarthritis is the most common articular disease. The problem with the OA therapeutic approach is that no curative treatments are known while there are also significant side effects associated with common OA treatments. Hence, many studies have been executed to find an effective therapeutic approach with fewer side effects. Participants in our survey were chosen amongst population of patients with a diagnosis of OA and could be labelled as primary OA since none of them had joint involvement atypical for OA (the elbow, wrist, shoulder, and MCP joints) as well as any evidence of chondrocal-

cinosis in their radiographic studies.

In our clinical trial the addition of colchicine to the common OA treatments culminated in significant improvement of symptoms and the greater response rate in post menopausal patients with OA of the knee over a 3-month period. The colchicine dose was well tolerated and there were no significant side effects associated with our therapeutic intervention compared with the control group. The observed tolerance in our study is in agreement with previous studies regarding the safety of this medication when used in appropriate dosage in patients with normal kidney and liver function (15).

The efficacy and safety of this new therapeutic approach has been already acclaimed by previous studies. Das, *et al*. asserted the efficacy of a regimen consisting of colchicine-nimesulide over a period of 5 months in patients with moderately severe symptomatic OA in their randomised controlled trial (16). They also conducted another clinical trial and acquired the same results showing significantly better symptom-modifying effects when colchicine was added to piroxicam plus intraarticular steroids over a 5-month period in patients with knee OA presenting with signs of inflammation (17).

Inflammation in OA is frequently secondary to the presence of calcium-containing crystals, that lead to the production of pro-inflammatory and catabolic mediators (nitric oxide (NO), MMP-13 and prostaglandin E2 (PGE-2) in human primary chondrocytes and synoviocytes (18) as well as interleukin-1 (IL-1), which is an important mediator of cartilage breakdown in OA (16). IL-1 and TNF-alpha, appear to be the major culprits in the pathogenesis of synovitis and in cartilage damage of the joint diseases. IL-1 stimulates the synthesis and secretion of MMPs that cause degeneration in OA (19). Calcium-containing crystals are frequently seen in severe OA (20-21). There are high levels of pyrophosphate (PP) in OA synovial fluid similar to CPPD patients that are directly related to the severity of degeneration in OA. The presence of CPPD causes biomechanical changes in extra-cellular matrix of cartilage and leads to
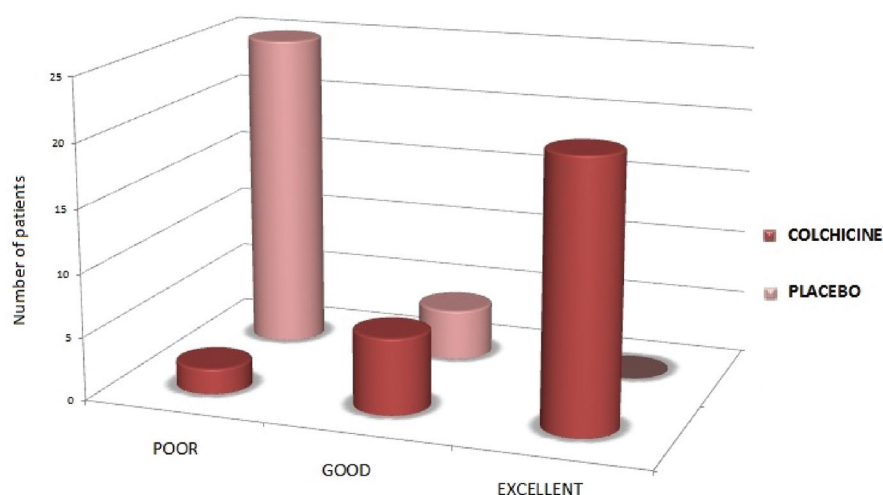
Fig. 2. Comparison of patients' global assessment in colchicine and placebo groups.
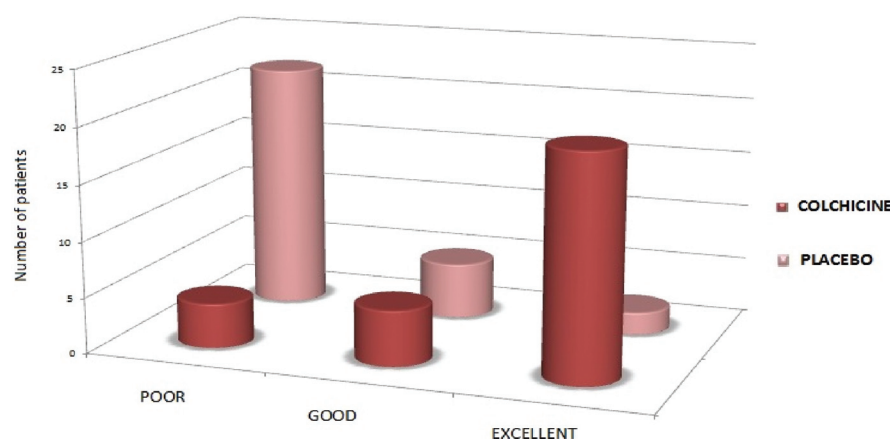

Fig. 3. Comparison of physician's global assessment in colchicine and placebo groups.

breakdown (3, 18, 22-23). It was previously thought that crystal deposition in OA is an on-off phenomenon, however, it is now understood that it both contribute to acute flares of inflammation as well as chronic low-grade, persistent inflammation in OA (16).

Colchicine inhibits urate crystal and calcium pyrophosphate crystal-induced inflammation. It detains microtubule assembly and inhibits many cellular functions. Inflammation is known to be caused in part by PGE1 and there are observations that claim colchicine acts as an anti PG agent. Additionally, it suppresses IL-1 beta processing and release, as well as L-selectin expression on neutrophils. It has been said that at low concentrations it can thwart the release of a crystal chemotactic factor from neutrophil lysosomes. It prevents the adhesion of neutrophiles to endothelial cells through diffusion of

adhesion molecules on the endothelium. There is evidence that supports its efficacy in preventing and treating gout and pseudogout flares. Therefore, it is hypothesized that colchicine can be effective in OA, based on the potential to prevent crystal-induced acute inflammatory flares (24-27).

However, since our study population did not show inflammation at baseline, perhaps another possible mechanism of action of colchicine is involved that they benefited from this treatment. It has been shown that colchicine inhibits elastase, a MMP in patients with COPD, which culminates in the prevention of emphysema in ex-smokers. As previously discussed, MMPs play an axial role in the degenerative joint processes; thus, it could be the eventual mechanism which needs further evaluation (8). There are also side effects associated with this therapeutical mo-

dality and it has a narrow therapeutic index. Gastrointestinal, hepatic, renal, neuromuscular, cerebral toxicity and bone marrow damage with high mortality are some of the associated accompanying side effects (9-10). However, no significant side effects were observed in our trial. Further research in this field, considering the usage of appropriate drug dosage will improve the understanding of the true pathogenesis of this condition, leading to exploration of an effective therapeutic approach for degenerative arthritis.

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