Efficacy of Colchicine in the Treatment of Primary Knee Osteoarthritis

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Abstract

The treatment of knee osteoarthritis is still difficult owing to the lack of a disease-limiting medicine and the scarcity of existing therapeutic interventions, which focus mostly on alleviating symptoms rather than addressing the underlying cause of the condition.Tostudy of the effectiveness of colchicine therapy in a group of patients with primary knee osteoarthritis is the focus of our research. Between the months of October 2020 and March 2022, fifty patients were admitted to the Orthopaedic outpatient clinic of the Medical Complex City of Mosul, Iraq. Each patient received a diagnosis of knee osteoarthritis (KOA) based on the standards established by the American College of Rheumatology (ACR). The participants were split into two separate groups after a random selection process. The observation period lasted for a total of sixteen weeks. Colchicine was given to patients in the first group (a total of 25), at a dose of 1 milligram per day, whereas patients in the second group (also a total of 25), received a placebo.At the 16th week of colchicine therapy, patients in Group 1 who received a colchicine treatment demonstrated a statistically significant decrease in their knee indices, as measured by the WOMAC Total 38.58 $\pm$ 6.7 (P= 0.05), VAS—overall pain 6.82 $\pm$ 1.63 (P= 0.05), and Doyle Index 4.74 $\pm$ 1.42 (P=0.003) scores, when compared to the baseline readings. Nevertheless, colchicine medication was well tolerated since no statistically significant difference in adverse events were noted between the colchicine and placebo groups.Our findings, which monitored VAS, Doyle indexalong with WOMAC indices in two groups of KOA patients, reveal that colchicine treatment is more effective than placebo in lowering symptoms of the condition.

Keywords: Knee Osteoarthritis (KOA), Colchicine, Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Visual Analogue Scale (VAS).

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Introduction

Osteoarthritis (OA) is a disease that may have several causes and is persistent and debilitating. It affects all joints and is characterized by damage to articular cartilage, ligaments, subchondral bone, joint capsules, and the muscle tissues that surround joints[1]. Knee osteoarthritis was found to be present in around 10-17% of persons over the age of 40, and in approximately 50% of adults over the age of 60[2-4]. In addition, the prevalence of this condition is higher in women than it is in males, and women also have a higher incidence of impairment [5].

Problem Statement

OA is currently the main contributor to disability, and it is predicted that it will soon overtake other factors as the main predictor of lifelong disability globally [6]. The socioeconomic impact of OA cannot be ignored because it not only leads to a decline in the quality of life, physical ability, and social participation of patients but also has a substantial financial impact on society [7]. The

most common site for osteoarthritis (OA) is the knee joint, and the main risk factors for developing knee OA are being older, having a history of injury, and being overweight [3, 7, 8]. Finding efficient methods to treat OA is a need that is not currently being met [7].

Aims of the Study

- To study the efficacy of Colchicine in the treatment of primary knee osteoarthritis.
- To assess the improvement in overall pain indices in Colchicine treated group.

Research Questions

- Is Colchicine therapy effective for the treatment of primary knee osteoarthritis (KOA)?
- Does Colchicine therapy show any improvement in overall knee pain indices in primary osteoarthritis patient?

Significance of the Study

A common progression of osteoarthritis is disability. Clinical signs have varying degrees of severity. However, they typically get worse, occur more frequently, and become more crippling. Knee osteoarthritis is initially managed conservatively when non-surgical therapeutic options are unsuccessful. Despite the fact that medications may help slow the progression of KOA and other inflammatory illnesses, there are currently no authorized disease-modifying therapies for the treatment of knee osteoarthritis.

Therefore, this study was designed to study the efficacy of drug that is reportedly used for KOA like Colchicine in the treatment of primary knee osteoarthritis.

Literature Review

Since ancient times, people have turned to colchicine for relief from a wide range of symptoms and conditions[9] [1]. Colchicine is one of the few drugs that were known throughout that historical period and have continued to be used up until the present day. Colchicine is a drug that is often used in modern medicine for the treatment of acute gout flares, prevention against gout flares, treatment of various crystal disorders etc. Colchicine has a wide-ranging anti-inflammatory action, which means that in addition to the purposes for which it is most generally recognized, it may also be beneficial for the treatment of number of other disorders[10].

Osteoarthritis is frequently a crippling condition that gets progressively worse over time. Clinical symptom severity may differ from patient to patient [11]. But over time, they almost invariably worsen, happen more frequently, and become more crippling. One's potential rate of development varies substantially from person to person. Clinical symptoms such as knee pain that develops gradually and gets worse with movement, knee edema and stiffness, pain after spending a lot of time sitting or resting, etc., are all common. Another typical clinical symptom is pain that worsens with time. Conservative therapy techniques are frequently used first when other non-surgical treatment options fall short in reducing the symptoms of knee osteoarthritis [12].

There are already a large number of medicines available for the treatment of OA; however, the majority of these treatments have adverse effects and limited efficacy. Colchicine's efficacy in treating gout and pseudogout, as well as avoiding inflammation brought on by calcium crystals, has garnered a lot of attention. There is evidence that uric acid has the ability to stimulate the innate immune response that is associated with OA [13]. In light of this, it has been postulated that colchicine may be useful in the treatment of OA, particularly OA of the knee. On the other hand, in recent years there has been debate on whether or not colchicine is an effective treatment for osteoarthritis. ThisWestern Ontario and McMaster Universities

(WOMAC) total scores, visual analogue scale for index knee pain (VAS-pain) and adverse events reported by patients will be used in this study to compare the effectiveness of colchicine in treating knee osteoarthritis (OA) with that of a placebo.

Methodology

Total of 50 patients with KOA were recruited for this study. The diseased knee underwent musculoskeletal ultrasonography, blood tests, radiography, and physical examinations for all of the patients.Age above 30, a confirmed case of knee osteoarthritis, a Kellgren- Lawrence (KL) score of 2 [14], and discomfort persisting more than 6 months were required for participation. Other rheumatic diseases, recent knee surgery, and infection of thejoint of knee made up the exclusion criteria.

The erythrocyte sedimentation rate (ESR) with C-reactive protein (CRP), were among the blood markers that were tested.

Study Endpoints

The major clinical response indicator was the percentage of patients who showed a 30% improvement (responder rate) in their overall WOMAC scores and VAS for the index knee pain after 16 weeks as compared to their respective baseline scores. The Western Ontario and McMaster Universities Arthritis Index (WOMAC), which has a score range of 0–20, stiffness of 0–8, and physical function of 0–68, was used to assess pain. The scale used to grade the questions was 0 for none, 1 for mild, 2 for moderate, 3 for severe, and 4 for extreme [15].The additional effectiveness endpoints were total pain (i.e., "How intense is pain wherever in your body"), patient rating of illness severity. Every end point was noted on a VAS. Additionally, Doyle's index was also noted[8]. On a 15-cm scale, all VAS scores were recorded.

Results and Treatment

Two groups of individuals were created at random. In the group 1, colchicine was given at a dose of 1 mg/day, whereas in the second group, placebo was given for 16-week duration of time.

There were 16 weeks of observation. At 8 and 16 weeks, the patients had follow-up exams. Every examination included the collection of VAS—overall pain and WOMAC data, and baseline and week 16 of the study includedDoyle Index and VAS Index Knee Pain.

The trial medicine was provided as capsules in bottles; each capsule included starch and 1 mg of colchicine. The placebo was given out in a similar pill that only contained starch.

Statistics Analysis

In this research study, categorical data was shown as frequency as well as percentage, on the contrary, continuous data was shown as mean $\pm$ SD. To compare the outcome measures of the study group at various follow-up times, a paired-t test was performed. To compare the variations between the colchicine and placebo groups, either the chi-square or Fisher exact test was performed.P-value with less than 0.05 was considered as statistically significant.

Results

In this study, there were a total of 50 participants, all of whom suffered from bilateral osteoarthritis of the knee. The overall number of research participants included 20 males (representing 40%) and 30 women (representing 60%). The 16-week follow-up period was successfully completed by all of the patients. The reported mean age of the patients were 67.64 ($\pm$4.81) years, and the duration of their illness was 28.06 ($\pm$8.89) months. In addition, tests for the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) were performed at the beginning of the study. The mean values for these two variables were 32.70 ($\pm$7.94) mm/hr and 32.02 ($\pm$7.47) mg/L, respectively. Table 1 reveals that

the patients also had a variety of comorbidities, including cardiovascular disorders (42 patients, or 84%), diabetes (30 patients, or 60%), and high blood pressure (41 patients, or 82.0%).

Before (as a baseline), after (8 weeks), and after (16 weeks) of the medicinal intervention, each participant's baseline pain indices were also collected. Mean values for the following indices were used as baseline readings: WOMAC Total 44.46 (±5.12), VAS Index Knee Pain 10.40 (±1.85), VAS—overall pain 7.80 (±1.63), and Doyle Index 5.20 (±1.44). The means of the WOMAC Total, VAS Index Knee Pain, VAS—overall pain, and Doyle Index at the end of the 8th week of intervention were 41.90 (±3.98), 9.02 (±2.05), 7.08 (±1.75), and 4.78 (±1.33), respectively. At 16 weeks, the mean values of the WOMAC Total 38.58 (±6.70), the VAS Index Knee Pain 8.50 (±2.34), the VAS—overall pain 6.82 (±1.64), and the Doyle Index 4.74 (±1.43) were once again recorded (Table 1).

Among the adverse responses that were recorded, patients experienced bloating, myalgia, an increase in knee pain, and an infection of the upper respiratory tract. According to the findings of our research, the side effects that were reported the most often were diarrhea, increased knee pain, and respiratory tract infections, each of which had a prevalence of 16 (32%), 13 (26%), and 13 (26%), respectively (Table 1).

Table 1. Demographic, laboratory data, clinical and Pain Indexes of the study group.

Gender		
	Frequency	**Percent**
Male	20	40
Female	30	60
Descriptive Statistics		
	Mean	**Std. Deviation**
Age in Years	67.64	14.81
Disease Duration (Months)	28.06	8.89
Erythrocyte Sedimentation Rate (mm/hr)	32.70	7.94
C-Reactive Protein (mg/L)	32.02	7.47
Other Comorbidities		
	Frequency	**Percent**
Hypertension	41	82.0
Diabetes	30	60.0
Cardiovascular Diseases	42	84.0
Baseline Pain Indexes		
	Mean	**Std. Deviation**
WOMAC Total	44.46	5.12
VAS Index Knee Pain	10.40	1.85
VAS—overall pain	7.80	1.63
Doyle Index	5.20	1.44

Pain Indexes at 8 Weeks		
	Mean	**Std. Deviation**
WOMAC Total	41.90	3.98
VAS Index Knee Pain	9.02	2.05
VAS—overall pain	7.08	1.75
Doyle Index	4.78	1.33
Pain Indexes at 16 Weeks		
	Mean	**Std. Deviation**
WOMAC Total	38.58	6.70
VAS Index Knee Pain	8.50	2.34
VAS—overall pain	6.82	1.64
Doyle Index	4.74	1.43
Adverse Events		
	Frequency	**Percent**
Diarrhea	16	32.0
Constipation	4	8.0
Bloating	5	10.0
Myalgia	9	18.0
Worsen Knee Pain	13	26.0
Respiratory Tract Infection	13	26.0

Table 1: Patients' demographic, clinical and pain assessment scores were recorded in mean ± standard deviation, frequency and/or percentage.
The Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Visual Analogue Scale index (VAS)

Colchicine was tolerated satisfactorily. Diarrhea and respiratory tract infection were the most prevalent side effects, however they were not significantly reported in colchicine-treated individuals (Table 2).

Table 2: Adverse Events of Colchicine Therapy

Adverse Events			
	Colchicine Group	**Placebo Group**	***p*-Value**
Diarrhea	10	6.0	0.225
Constipation	4	.0	0.11
Bloating	3	2.0	1
Myalgia	6	3.0	0.463
Worsen Knee Pain	5	8.0	0.333
Respiratory Tract Infection	8	5.0	0.333

Table 2: Adverse events were recorded for both Colchicine therapy group and Placebo. Chi-square test or Fisher exact test was used to compare the difference between two groups with 95% Confidence Interval. P-value with < 0.05 was considered statistically significant.

During the course of the clinical trial and within 16 weeks of the last dose of the investigational drug being given out, there was not a single patient who had an adverse event that led to their death or hospitalization. In none of the two groups was there any substantial abnormality discovered in the laboratory. There was not a single patient who was discharged from their treatment as a direct result of any unfavorable drug-related adverse effects. Additionally, oral colchicine was shown to be well tolerated, and the investigation discovered no cases of any negative effects related with the administration of the drug.

The recordings from the baseline were compared with the pain indices that were collected at the initial evaluation, as well as during the eighth and sixteenth weeks of the study. All indices, including the WOMAC Total, the Doyle Index, the VAS Index Knee Pain, and the VAS—overall pain, significantly changed at the 8th and 16th weeks of medical treatment and colchicine medication. Table 3 compares the results between the colchicine group and the placebo group in terms of the outcomes that were evaluated.

Table 3: Outcome Measures: Comparison of baseline and Week 26th Pain Indices of Colchicine therapy

	Baseline	At Week 8	At Week 16
WOMAC Total	44.46 + 5.11	41.9 + 3.97 (P=0.003)	38.58 + 6.7 (P= <0.05)
VAS Index Knee Pain	10.4 + 1.85	9.02 + 2.04 (P= <0.05)	8.5 + 2.34 (P= <0.05)
VAS—overall pain	7.8 + 1.62	7.08 + 1.74 (P= <0.05)	6.82 + 1.63 (P= <0.05)
Doyle Index	5.2 + 1.44	4.78 + 1.32 (P= <0.05)	4.74 + 1.42 (P=0.003)

Table 3: Comparison of colchicine therapy outcome measures at 8th and 16th week with baseline pain indices scores by using paired-t test. P-value <0.05 was considered statistically significant.
The Western Ontario and McMaster Universities Arthritis Index (WOMAC) and Visual Analogue Scale index (VAS)

Discussion

Colchicine has been investigated in several studies, with varied outcomes regarding its effectiveness in symptom alleviation. Despite the possibility that medicines might assist postpone the progression of osteoarthritis-related problems, there are currently no disease-modifying therapies that have been licensed for the KOA treatment.

A research by Leung et al. on 109 participants showed that colchicine was ineffective in reducing knee osteoarthritis symptoms and inflammation (COLKOA trial), unable to achieve the expected result over a period of 16-week when compared to a placebo. This finding is inconsistent with the one from our investigation. In comparison to the group receiving placebo, we discovered that the group receiving colchicine showed a statistically significant decline in WOMAC Total 38.58 $\pm$ 6.7 (P= <0.05), VAS—overall pain 6.82 $\pm$ 1.63 (P= <0.05), and Doyle Index 4.74 $\pm$ 1.42 (P=0.003)) ratings at 16 weeks[16].

Even though colchicine is a safe alternative for treating knee osteoarthritis, a meta-analysis done in 2021 that examined six randomized placebo-controlled trials and one non-placebo-controlled trial found no statistically significant differences between colchicine and a placebo in terms of management of pain and significant functional improvement, which is denied by our study[17]. In our study, there was significantly decrease in the VAS index for knee pain i.e. 8.5 + 2.34 (P= <0.05)

Additionally, it wouldn't assist in reducing knee pain, stiffness, or function. This runs counter to the advice to take oral colchicine, which has been shown to reduce pain intensity in four trials [12, 18–20] and to enhance physical function in another three [12, 18, 20]. Even so, oral colchicine is generally safe when compared to placebo, and 1 mg a day of oral colchicine

might be a reasonable dose for the treatment of patients of knee OA.Colchicine-receiving individuals in our research demonstrated comparatively more adverse events than placebo patients, however the difference was not statistically significant.

In recent studies findings indicated a decrease of both indices, colchicine may lessen patients' knee discomfort, stiffness, and function, although no statistical difference was detected between two groups[18-21]. Participants in numerous studies were given colchicine 0.5 mg twice day to test for safety. When VAS-pain was taken into consideration, there was no difference in the scores for colchicine (p = 0.08)[16, 18, 19]. However, in our investigation, we discovered a statistically significant change between the VAS overall pain scores at week 16 and the baseline values.

In one study, 64 study participants (10 lames and 54 females) with hand OA and ages 40 to 80 were allocated to receive colchicine (0.5 mg, two times a day) or a corresponding placebo for a period of 12 weeks[1]. As there was no difference between the colchicine and placebo groups, they concluded that colchicine was unable to decrease pain of hand as measured by VAS and hematological test results such C-reactive protein. Therefore, the findings of Davis and colleaguesopposed the use of colchicine for the symptomatic treatment of OA of hands[1].

Colchicine therapy for the treatment of KOA is controversial, despite the fact that a lot of study results are against it. Large-scale research is thus required to better illuminate the potential medical benefits of colchicine.

Conclusion

The primary result of this research was that OA patients' knee pain was greatly decreased after taking oral colchicine. Additionally, given the significant improvements in the overall WOMAC and VAS indices, it might be beneficial for reducing knee ache. This runs counter to the advice that oral colchicine may lessen pain intensity and is backed by a number of research. Oral colchicine is nonetheless often safe and well tolerated.

Recommendations

For future perspective, a large sample size along with large scale studies are necessary in order toassess the efficacy, potency, safety window, and treatment duration of colchicine therapy. This indicates that additional large scale and more number of samples randomized control trials are required in order to validatethis study findings.

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