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# Comparison between oral colchicine and placebo for the treatment of osteoarthritis in Iraqi patients

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**Running title**: Oral Colchicine vs Placebo in Iraqi Knee Osteoarthritis Treatment

**Abstract**
**Background:** Treating knee osteoarthritis (OA) has always provided a challenge this is because there are impartial a few effective treatments available that will standstill the advancement of the disease, and also because standing therapies generally address care of the symptom rather than stopping progression of the ailment.
**Objectives** : To judge the effects of colchicine and a placebo in Iraqi individuals suffering from knee OA
**Methods**: In a three-month double-blind, parallel-group study, 80 patients (69 females and 11 males) with knee OA were indiscriminately assigned to obtain either 1 mg of colchicine or 1 mg of starch as a placebo. The study's instruments included WOMAC, VAS, investigator global assessment using a Likert scale, and patient global assessment to measure pain indices.

**Results**: Individuals who established colchicine adage a statistically substantial decrease in their knee indices (WOMAC scale: 19.6, p-value: 0.035) and VAS score (29.3) (p-value: 0.015). During the first month, the patient's global rating was (3), with a p-value of less than 0.001, whereas the investigator's global assessment, using the Likert scale, was none (8), mild (13), moderate (13), severe (4), and extremely severe (1). With the exception of the patient global evaluation in Month 2, which remained statistically substantial (p-value = 0.018) when compared to baseline readings, no statistically significant changes were seen in Months 2 or 3.

**Conclusion**: Patients with OA in their knees who acquired colchicine showed a remarkably higher grade of symptom relief than those in the control group who received a placebo
**Keywords**: Colchicine, Osteoarthritis, Placebo, VAS, WOMAC, Likert scale.

## Introduction

The pathophysiological and morphological amendments in joint tissues that occur with OA embrace the deterioration of cartilage, resorption of bone, and development of osteophytes. Symptoms such as pain, stiffness, edema, and decreased joint functionality are caused by the year (Allen et al., 2022). By 2020, 595 million people worldwide—roughly 7.6% of the total world population—were sorrow from OA (Hao et al., 2024). Osteoarthritis can be characterized as the final consequence of various processes that terminate in joint degeneration (Omar et al., 2021) .Knee OA affects about 21% of people in Iraq; for those with a body mass index (BMI) of 30 kg/m or greater, the risk rises to 53%(AL-Barzinjy, 2010). ). The knee is the utmost ordinarily pretentious joint in OA (Al-Rawi et al., 2011). Age, obesity and gender (women) are significant apparatuses in the development of (OA)(Blagojevic et al., 2010; O'Brien & McDougall, 2019;

Shumnalieva et al., 2023). Utmost patients with OA experience low-grade inflammation, which plays a noteworthy role in the development and evolution of the disease (Barreto et al., 2020; van den Bosch, 2021). ). Pro-inflammatory mediators, together with cytokines, lipid mediators, and reactive oxygen species (ROS) created by chondrocytes, synoviocytes, and osteoblasts, interrupt anabolic processes and endorse the release of proteolytic enzymes, This clues to the deprivation of the extracellular matrix and bestows to cartilage loss(Zahan et al., 2020). Utmost KOA medications highlighting more on symptom respite than on addressing the underlying cause of the problem (Qaryaqos et al., 2022). Grander sternness of knee OA has been accompanying with elevated uric acid levels in the synovial fluid. In a similar vein, the accumulation of mono-sodium uric acid (MSU) in the joints can impact the proclamation of cytokines during inflammation. Notably, inflammation interrelated to osteoarthritis (OA) of the knee is repeatedly interrelated to the crystals of calcium pyrophosphate dihydrate (CPPD), which increases the fusion of IL-1. this cytokine is essential for the cartilage to break down in OA(Singh et al., 2023). Contemporary treatments mainly proposition short-term symptom respite and often fail due to ineffectiveness and substantial side effects (Jawad et al., 2011).

Colchicine, a natural alkaloid consequential from various plants of the Colchicine family, like Colchicum autumnale, demonstrations antifibrotic and anti-inflammatory physiognomies. It has been used for many years to treat pericarditis, familial Mediterranean fever, gout, and extra inflammatory and dermatologic complaints(Singh et al., 2023).Colchicine recently gotten attention for its potential role in managing knee (OA) , Colchicine has grossed a lot of attention, which suggests it will treat the illness because of its effectiveness in treating gout and pseudogout as well as in tumbling inflammation conveyed on by calcium crystals (KOA). Furthermore, studies bring up that uric acid can participate to the induction of the innate immune response concomitant with OA(Grässel & Muschter, 2020). It has been established in the past that colchicine effectively condenses inflammation brought on by the realization of calcium crystals(Slobodnick et al., 2018) .

## Patients and methods

### Study design and patient selection

This three-month randomized, double-blind study with comparable groups established approval from the University of Baghdad's ethics committee and was conducted in an outpatient clinic. Participants were apportioned to obtain either 1 mg of colchicine or a placebo. A physician managed patient apportionment and capsule supervision. A standardized construction of colchicine was repackaged, and comparable placebo tablets were formed to ensure allocation concealment. The physician allotted colchicine or placebo in numbered bottles conferring to a randomization list generated by the biostatistician. Participants were indiscriminately assigned in blocks of ten to either the colchicine group or the placebo group, adhering to a 1:1 ratio. Both the researcher assessing patients at baseline and during follow-ups (at Months 1, 2, and 3) and the patients themselves were blinded to the distinctiveness of the capsules.

### Clinical evaluation

### Western Ontario McMaster University Osteoarthritis (WOMAC) index

An Arabic style of the WOMAC index was exploited to evaluate knee pain, stiffness, and physical function. Three subscales encompass the 24 items in this self-administered questionnaire: physical function (17 items, score range 0-68), stiffness (2 items, score range 0-8), and pain (5 items, score range 0-20). The overall normalized WOMAC total score was attained by uniting the normalized subscale values. Patients were given the WOMAC (questionnaire at the start of the study and at

months 1, 2, and 3). The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) is a universally used patient-reported consequence extent for evaluating OA in the lower edge (Walker et al., 2019).

**Visual analog scale (VAS)**

The pain severity was weighed using a Visual Analog Scale (VAS) extending from 0 to 100 mm. In this study, the investigator examined patients, "Built on VAS, how much pain are you experiencing?" During Consequent visits, the researcher inquired about their pain again, using the VAS).

**Investigator global assessment (IGA)**

The disease activity was restrained using a Likert scale with five ranks: none (no symptoms and no constraints in daily activities), mild activity (mild symptoms and no restrictions of normal daily activities), moderate activity (modest symptoms and restrictions in some daily activities), severe activity (severe symptoms and inability to achieve most daily activities), and very severe.

**Statistical analysis plan**

Categorical encouragements such as sex, smoking status, and IGA were concise using frequencies and proportions. Quantitative factors such as age, weight, pain VAS score, and PGA were concise using medium and interquartile range (IQR). The WOMAC score was concise with the mean and standard deviation (SD), and normality was checked using the Shapiro-Wilk test.

The expenditure and construal of arithmetical analyses to inspect relationships are precarious components of biological research. Statistical investigates frequently employ the P value to show these links. (Thiese et al., 2016).

The P value has conquered significant rank, rendering it familiar to nearly all researchers, particularly the edge of "$P < 0.05$" as a indicator of "statistical significance." (Andrade, 2019).

The chi-square test was exploited to ascertain whether statistically significant differences occurred in gender, smoking status, and IGA among the analyzed groups. The independent samples t-test was employed to determine statistically significant differences in age, weight, WOMAC score, VAS score for pain, and PGA among the study groups.

The independent samples t-test was exploited to estimate significant differences between the study groups concerning age, weight, WOMAC score, VAS pain score, and PGA. An intent-to-treat analysis was executed, employing the last observation carried forward technique to discourse missing data. Statistical analysis was accompanied utilizing Jamovi version 2.3.26 for Windows.

**Results**

The study included eight patients. Both clusters, the placebo group and the colchicine group, consist of 40 patients. Table 1 presents their clinical and demographic characteristics.

**At the starting point**

Table 1 elucidates a comparison between the investigational group (Colchicine group) and the control group across numerous parameters. No statistically substantial differences occurred between the two crowds at standard regarding demographic and clinical variables.

**Table 1 Shows the demographic and clinical characteristics of study population at baseline.**

| Variable | Experimental group (n=40) | Control group (n=40) | *P* value <0.05 |
|---|---|---|---|
| Gender (Female) | 34 (85%) | 35 (87.5) | 0.745 |
| Age (Years) | 61.3 (11.94) | 61.1 (9.6) | 0.934 |
| Weight (Kg) | 87.5 (17.5) | 88.5 (12) | 0.806 |
| WOMAC score | 39.52 (11.95) | 42.13 (13.82) | 0.371 |
| VAS score for pain | 55.88 (15.44) | 56 (14.29) | 0.97 |
| IGA by Likert scale | Mild=7 (17.5%)<br>Moderate=22 (55%)<br>Severe=10 (25%)<br>Very severe=1 (2.5%) | Mild=4 (10%)<br>Moderate=20 (50%)<br>Severe=16 (40%)<br>Very severe=0 (0%) | 0.348 |
| IGA by VAS | 5.53 (1.53) | 5.58 (1.54) | 0.884 |
| PGA by VAS | 7 (1.5) | 8 (1.13) | 0.116 |

**n**: number of cases: **WOMAC**: Western Ontario McMaster University Osteoarthritis index; **VAS**: Visual Analogue Scale; **IGA**: Investigator Global Assessment; **PGA**: patient global assessment; $p < 0.05$ is reflected statistically substantial.

**WOMAC score**

The outcomes of a clinical trial contrasting the effectiveness of Colchicine against placebo in (reducing symptoms measured by the WOMAC index over a period of three months are shown in Table 2).

**Table 2 comparison of WOMAC INDEX at each time point for the colchicine group and the placebo group**.

| WOMAC score | Colchicine (n=40) | Placebo (n=40) | *P* value |
|---|---|---|---|
| Month 1 | 19.6 (18.3) | 28.8 (20.3) | 0.035 |
| Month 2 | 22.7 (16.8) | 30.3 (21.1) | 0.078 |
| Month 3 | 24.4 (16.8) | 28.8 (20.3) | 0.289 |

**WOMAC:** Western Ontario McMaster University Osteoarthritis index; n: number of cases; $p < 0.05$ is considered statistically significant.

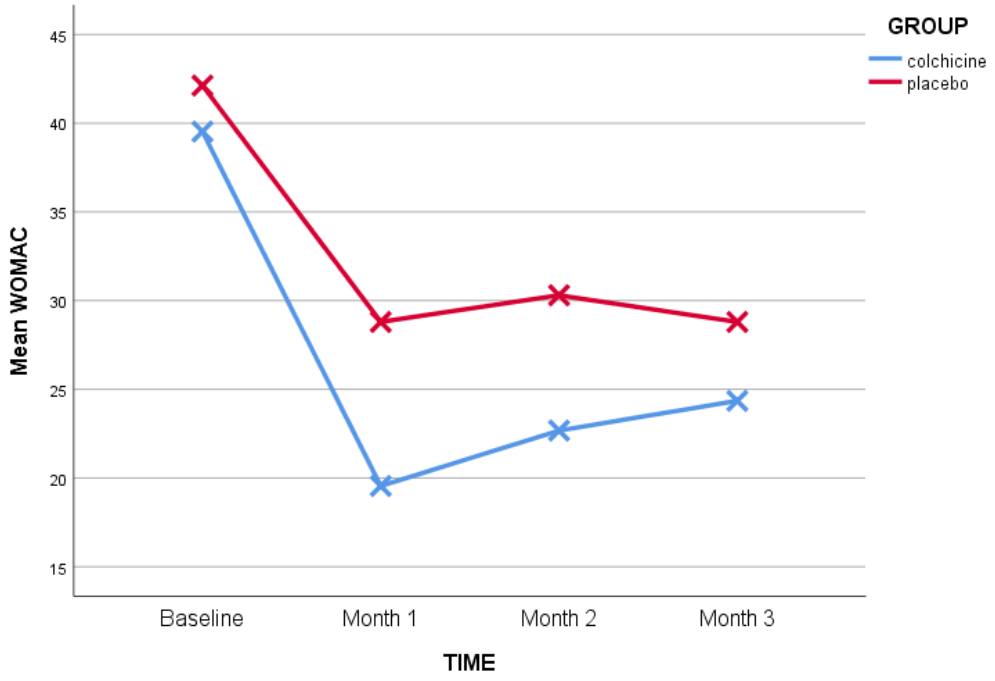


**Figure 1: WOMAC mean at each point for colchicine group and placebo group.**

**VAS score**

The consequences contrasting the efficiency of colchicine against placebo in tumbling pain as (restrained by the VAS over a period of three months are shown in Table3).

**Table 3: comparison of vas score for pain between the studied groups.**

| VAS score for pain | Colchicine (n=40) | Placebo (n=40) | *P* value |
|---|---|---|---|
| Month 1 | 29.3 (22.8) | 41.8 (22.3) | 0.015 |
| Month 2 | 33.7 (20.5) | 42.3 (22.5) | 0.082 |
| Month 3 | 36.4 (20.6) | 42.3 (22.5) | 0.232 |

**VAS:** Visual Analogue Scale; **n:** Number of cases; $p < 0.05$ is well thought-out statistically substantial.

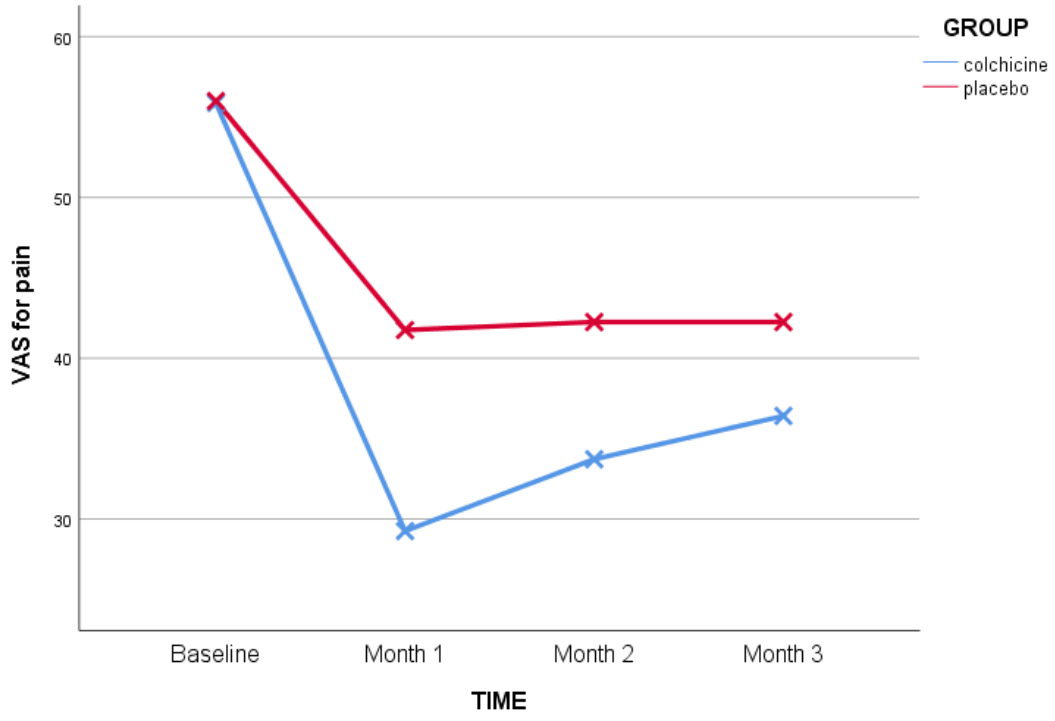


**Figure 2: VAS score for pain for the studied groups at every period point likert scale**

The outcomes of evaluating the efficacy of Colchicine compared to placebo in diminishing disease activity, as measured by the Investigator Global Assessment (IGA) on a Likert scale for a duration of three months. were shown in Table 4 .

**Table 4: Comparison of investigator global assessment between the studied groups**

| IGA by Likert scale | Colchicine (n=40) | Placebo (n=40) |
|---|---|---|
| Month 1 | None=8 (20%)<br>Mild=14 (35%)<br>Moderate=13 (32.5%)<br>Severe=4 (10%)<br>Very severe=1 (2.5%) | None=3 (7.5%)<br>Mild=6 (15%)<br>Moderate=20 (50%)<br>Severe=11 (27.5%)<br>Very severe=0 (0%) |
| Month 2 | None=5 (12.5%)<br>Mild=14 (35%)<br>Moderate=16 (40%)<br>Severe=4 (10%)<br>: :Very severe=1 (2.5%) | None=3 (7.5%)<br>Mild=6 (15%)<br>Moderate=20 (50%)<br>Severe=11 (27.5%)<br>Very severe=0 (0%) |
| Month 3 | None=5 (12.5%)<br>Mild=10 (25%)<br>Moderate=20 (50%)<br>Severe=4 (10%)<br>Very severe=1 (2.5%) | None=3 (7.5%)<br>Mild=7 (17.5%)<br>Moderate=17 (42.5%)<br>Severe=13 (32.5%)<br>Very severe=0 (0%) |

**IGA:** Investigator Global Assessment; **n:** Number of cases; $p < 0.05$ is well thought-out statistically substantial.

**Patient global assessment**

The outcomes of evaluating the efficacy of Colchicine compared to placebo in mitigating illness severity, as measured by the Physician Global Assessment (PGA) utilizing the Visual Analog Scale (VAS) over a three-month duration. are shown in Table5 .

**Table 5: Comparison of patient global assessment between the studied groups.**

| Patient global assessment | Colchicine (n=40) | Placebo (n=40) | *P* value |
|---|---|---|---|
| Month 1 | 3 (5) | 7 (4) | <0.001 |
| Month 2 | 4 (3) | 7 (4) | 0.018 |
| Month 3 | 4.5 (2) | 7 (4) | 0.064 |

**n:** Number of cases; $p < 0.05$ is considered statistically substantial

**Adverse effects**

During the initial month, eight individuals had nausea and diarrhea, while five patients reported abdominal pain.

**Discussion**

Patients with knee osteoarthritis had heightened symptom control with colchicine during the course of a three-month period. A much larger measurement of patients in the colchicine group had enhanced performance on the primary assessment measures. Furthermore, a statistically significant difference be present between the mean values of the colchicine and placebo groups. The current study indicates that individuals with knee osteoarthritis who use oral colchicine (1 mg) for alleviation of pain and stiffness also report enhanced physical activity. The current study indicated that eight individuals experienced nausea and diarrhea, while five patients reported stomach pain during the initial month. The favorable outcomes of colchicine in knee osteoarthritis can be elucidated. Monosodium uric acid (MSU) buildup in joints can influence the production of inflammatory cytokines. Crystals of calcium pyrophosphate dihydrate (CPPD), which stimulate IL-1 production, are often found alongside inflammation associated with osteoarthritis (OA) of the knee. This cytokine is crucial for cartilage degradation in osteoarthritis.(Singh et al., 2023). Tyrosine generated by microcrystals is phosphorylated by this drug, which reduces inflammation in patients. Colchicine additionally inhibits a matrix metalloproteinase (MMP) known as elastase. Colchicine is so largely regarded as capable of alleviating symptoms and altering the progression of the disease in people with osteoarthritis. (Aran et al., 2011). Colchicine suppresses the NLRP3 inflammasome, a crucial component in inflammation. By diminishing inflammation, colchicine may relieve pain and enhance joint function in osteoarthritis. (Amaral et al., 2023). Colchicine also plays a role in reducing oxidative stress, which contributes to cartilage breakdown in osteoarthritis. Colchicine possesses antioxidant effects that may mitigate oxidative damage.(Singh et al., 2023). Autophagy modulation is a cellular process that facilitates the removal of damaged components. Colchicine may affect autophagy, potentially facilitating the elimination of damaged cartilage and enhancing tissue healing.(Seiliez et al., 2016). Colchicine influences chondrocyte metabolism; chondrocytes are the cells responsible for cartilage formation and maintenance. Colchicine may change chondrocyte metabolism, potentially diminishing cartilage breakdown and facilitating healing.(Leung et al., 2015).

The VAS-pain and the WOMAC total index were used as the primary consequence events. The Visual Analog Scale (VAS) is commonly employed to evaluate pain and is recognized for its validity, responsiveness, dependability, and reliability. The WOMAC index is the most often utilized outcome measure in osteoarthritis investigations, particularly concerning the lower extremities. The WOMAC OA index has demonstrated reliability, feasibility, and sensitivity to

changes in the conditions of OA patients following various medications in several trials (Bellamy et al., 1988).

The data analysis consequences point out no statistically substantial differences between the investigational and controller groups at starting point across all variables (sex, age, weight, WOMAC, VAS, IGA by Likert scale, and PGA), with Pvalues exceeding 0.05 for each variable. This indicates that the two crowds were comparable before to the intervention, facilitating an impartial evaluation of the intervention's outcomes.

**WOMAC score**

The three-month WOMAC ratings for individuals administered colchicine compared to those given a placebo. Patients with osteoarthritis are evaluated for ache, rigidity, and physical function utilizing the WOMAC score. Superior outcomes are signified by diminished scores. The mean WOMAC score for the colchicine group was 19.6, whereas the mean WOMAC score for the placebo group was 28.8 (p value = 0.035). At the assumption of the initial month, the colchicine group exhibited markedly lower WOMAC scores relative to the placebo group, signifying superior symptom reduction. A P- value of 0.035 designated that this transformation was statistically substantial at Month 1.Additionally, Month 2 designated that the WOMAC mean score for colchicine was 22.7, whereas the WOMAC mean score for the placebo group was 30.3. (p- value = 0.078).

At the conclusion of the second month, the colchicine group maintained lower WOMAC ratings compared to the placebo group. Nonetheless, the P- value of 0.078 suggests that this difference lacked statistical significance, while it exhibited a tendency towards significance.

Furthermore, the WOMAC mean score for the colchicine group in Month 3 was 24.4, whereas the placebo group had a score of 28.8. ( p- value =0.289).

Consequently, by the conclusion of the third month, the disparity in WOMAC scores between the colchicine and placebo groups diminished. The colchicine set demonstrated lower grooves; however, the P value of 0.289 signposted that this dissimilarity lacked statistical significance.

**VAS score**

The data analysis revealed that the mean VAS score for colchicine was 29.3, while for placebo it was 41.8 (P value = 0.015). Consequently, the mean pain score during the initial month for the colchicine group was markedly lower than that of the placebo group. A p-value of 0.015 signifies a statistically substantial dissimilarity between the two sets at the standard alpha level of 0.05. This specified that colchicine was obliging in alleviating pain comparative to placebo during the preliminary month. During months 2 and 3, the p-value surpassed 0.05, indicating no significant dissimilarity.

A 2016 study in Iraq involving 150 patients shown that both paracetamol alone and paracetamol in conjunction with colchicine effectively alleviated symptoms of primary knee osteoarthritis, including pain, stiffness, physical function, and the overall WOMAC score. The incorporation of colchicine with paracetamol yields enhanced symptomatic relief and prolongs the duration of effect relative to paracetamol used in isolation. (Salman & Rafea, 2016) .

The endorsement for oral colchicine administration is substantiated by data from three trials. (Aran et al., 2011; Das et al., 2002; Yusuf, 2016), which have indicated a reduction in pain intensity, and three trials (Yusuf 2016; Das, Mishra et al. 2002; Aran, Malekzadeh et al. 2011) that have

confirmed its efficacy in enhancing physical function. Moreover, oral colchicine is generally regarded as safe relative to placebo, with a daily dosage of 1 mg being well-tolerated and potentially suitable for the treatment of individuals with knee OA. (Qaryaqos et al., 2022).

Recent studies suggest a reduction in these indicators, demonstrating that colchicine may alleviate knee pain, stiffness, and improve functionality in patients. However, no statistically substantial difference was seen among the two crowds.. (Das et al., 2002) (Liu et al., 2022).
Multiple trials involved people receiving colchicine at a dosage of 0.5 mg bi-daily to assess its safety. No significant difference was detected in VAS-pain scores for colchicine.($p = 0.08$)(Das et al., 2002).

The investigated data revealed a statistically substantial difference between the global VAS pain scores and the baseline values.
A comparable study was conducted at the Orthopedic Outpatient Clinic at the Medical Complex in Mosul, Iraq. Fifty individuals were randomly allocated to two groups for a sixteen-week observation duration. The first batch of 25 patients received a daily dosage of 1 mg of colchicine, whereas the second cohort, also including 25 patients, was given a placebo. Colchicine demonstrated a statistically significant improvement in knee parameters.. (Mohanad Adnan Bakr Mohammed, 2022).this study also showed similar findings.

In dissimilarity to the present findings, A inquiry by Leung et al. in Singapore exposed that colchicine was ineffective in mitigating symptoms or lowering inflammation related to knee osteoarthritis during a 16-week period. The results indicated no substantial dissimilarity between colchicine and placebo, in dissimilarity to the findings of the contemporary study. Leung, 2018. This may be attributable to various influences. Leung et al. accompanied a study designating that colchicine is ineffectual in alleviating the symptoms of knee osteoarthritis. They reported a greater response in the placebo group paralleled to the colchicine group. Consequently, any enhancements in the colchicine group will be challenging to identify, which may elucidate why Leung et al. did not observe comparable outcomes as in our investigation.(Leung et al., 2018) .

A meta-analysis of six randomized placebo-controlled trials and one non-placebo-controlled trial revealed no statistically substantial dissimilarities in pain management or Notable functional enhancement between colchicine and placebo(Singh et al., 2022),
This inquiry contests these findings. A meta-analysis demonstrated colchicine's unsuccessfulness non treating symptoms of knee osteoarthritis. A credible explanation for the noted poor efficacy is the inadequate research focused on a certain subgroup of knee osteoarthritis patients exhibiting local or systemic inflammation, who may exhibit a more positive reaction to colchicine. Das et al. identified patients displaying a minimum of double out of four clinical signs of inflammation: joint temperateness, discomfort along the joint margin, synovial effusion, and soft tissue edema around the knee, and found that colchicine had a beneficial impact on knee symptoms.(Das et al., 2002) .

Gastrointestinal complications, such by way of motion sickness( nausea), gagging(vomiting), and notably dose-dependent diarrhea, are the most prevalent adverse effects of colchicine, affecting 5–10% of patients. (Angelidis et al., 2018), similar side effects exist with the current study.

The primary merits of the current investigation were the randomly selected subjects. A physician not engaged in data collecting and analysis, tasked with capsule distribution. The author, unaware of the group randomization, gathered and examined all the data.

.The study's shortcomings were a imperfect sample size. Histological and blood samples were not obtained nor evaluated, and radiographic examinations were not conducted during follow-up. The present study relied on self-reported questionnaires to evaluate pain and physical functioning, which may introduce bias due to possible mistakes in reporting.

**Conclusion:** The principal outcome of this study was that knee pain in osteoarthritis patients significantly decreased with the administration of oral colchicine. The substantial improvements in the overall WOMAC and VAS scores suggest its potential effectiveness in reducing knee pain.

**Recommendations:** Future large-scale studies with an expanded sample dimensions are essential to assess the efficacy, potency, safety profile, and recommended treatment duration of colchicine therapy. This indicates that additional randomized controlled trials with larger samples are necessary to corroborate the findings of this investigation.

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