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Colchicine is an effective therapeutic agent in erosive hand osteoarthritis

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Ethics Committee Approval
The study was approved by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (decision date: April 7, 2023; decision number: 2023/193).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The efficacy of colchicine has been assessed in hand osteoarthritis; however, no studies have investigated its use in the more severe subtype of hand osteoarthritis, known as erosive hand osteoarthritis (EHOA). This retrospective cohort study investigated whether colchicine therapy could provide symptomatic relief and improve inflammation markers in patients with EHOA.
Methods: The study included a total of 43 EHOA patients using colchicine (2×0.5 mg) + paracetamol (3×500 mg) daily (colchicine group) and 43 EHOA patients using only paracetamol (3×500 mg) (standard therapy group). Both groups were evaluated for various parameters.
Results: The groups were similar in terms of age, sex distribution, and other sociodemographic variables. The decreases in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels from baseline were significantly greater in the colchicine group (P<0.001). Additionally, the visual analog scale (VAS) and Australian Canadian Osteoarthritis Hand Index (AUSCAN) scores, which include pain, stiffness, function, and total score, were significantly better in the colchicine group at 3 months compared to the standard therapy group (P<0.001). Furthermore, although both groups showed significant improvements in these parameters, the amount of improvement was significantly greater in the colchicine group (P<0.001).
Conclusion: The combined use of colchicine and paracetamol improved CRP and ESR levels, VAS score, and all AUSCAN scores in patients with EHOA. Moreover, these benefits were significantly greater than standard therapy with paracetamol alone. Colchicine appears to be an effective therapeutic agent in the treatment of EHOA.

Keywords: erosive hand osteoarthritis, colchicine, Australian Canadian Osteoarthritis Hand Index, visual analog scale, erythrocyte sedimentation rate, C-reactive protein

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Introduction

Osteoarthritis is the most prevalent type of arthritis worldwide, affecting nearly 10% of males and 18% of females aged 60 and above [1,2]. The knee joints are the most commonly affected, followed by the joints of the hands and hips [3]. Hand osteoarthritis (HOA) is particularly common among older populations, with a prevalence of up to 80%, and typically presents with mild symptoms [4].

Three types of HOA have been described: erosive HOA (EHOA), nodal or non-erosive HOA (non-EHOA), and first carpometacarpal joint osteoarthritis [3]. EHOA is the most aggressive form and is estimated to occur in 2.8% of individuals older than 55 years [4]. It presents with an acute onset of pain, joint swelling, and redness (Figure 1). Radiological findings include central joint erosion, gull-wing lesions (saw-tooth appearance), collapse of the subchondral bone, marginal osteophytes, and, rarely, ankylosis (Figure 2) [3,5]. The debate remains on whether EHOA should be considered a completely different type of HOA or a more serious clinical form of non-EHOA [5]. However, it is established that individuals with EHOA experience more severe hand pain and have a higher risk of disability and joint deformity, resulting in worse health-related quality of life compared to subjects with non-EHOA [6,7]. Only a few effective treatments for EHOA address symptoms but have no known benefit in preventing the disease or limiting its progression [4,5]. Although the pathophysiology of EHOA is not fully understood, these data suggest that EHOA differs from non-EHOA in its pathophysiology, which could warrant differences in management [4].

Figure 1: Clinical features of erosive hand osteoarthritis: Demonstrating soft swelling (marked by asterisks) of the proximal and distal interphalangeal joints. Demonstrating deformity and bony enlargement (nodes) of proximal and distal interphalangeal joints (marked by arrows). Subluxation at the interphalangeal joint levels (highlighted by the red lines)

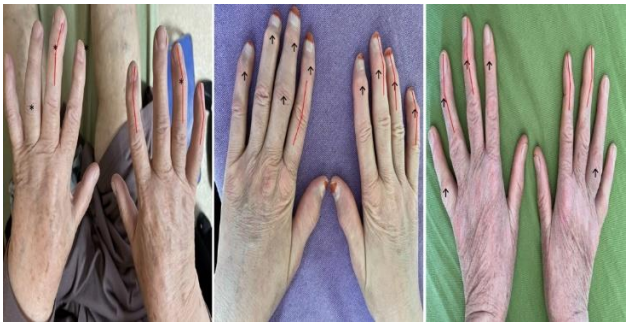
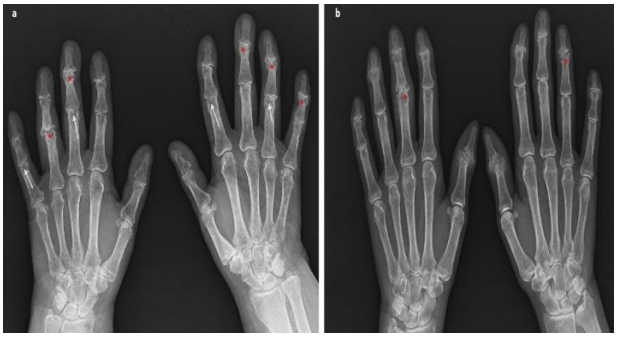


Figure 2: Radiological features of erosive hand osteoarthritis (EHOA): a. Radiograph EHOA, demonstrating 'gull-wing' appearance (red asterisks) and joint-space narrowing (white arrows). b. Radiograph of EHOA, demonstrating 'saw-tooth' appearance (red asterisks)



The possible pathological link between uric acid and osteoarthritis has been a long-standing topic of research [8,9]. Monosodium urate crystals have shown a strong association with cartilage degeneration and lesions [10]. Colchicine, an anti-inflammatory agent primarily known for its mechanism of action involving tubulin disruption and anti-mitotic effects, leading to the downregulation of multiple inflammatory pathways and modulation of innate immunity, has been well-established in gout and familial Mediterranean fever treatment [11]. Furthermore, ongoing investigations are exploring the potential therapeutic roles of colchicine in rheumatic diseases like osteoarthritis and Behçet's disease, as well as non-rheumatic conditions such as pericarditis, atherosclerosis and liver cirrhosis [11].

Studies on the use of colchicine in knee osteoarthritis have presented inconsistent results [12–15]. On the other hand, to the best of our knowledge, only two studies have been conducted so far on the use of colchicine in HOA, which did not report positive results [2,16]. One potential limitation of these studies is that they enrolled both EHOA and non-EHOA patients, which could have obscured the potential beneficial effects, specifically in patients with EHOA [2,16].

We hypothesized that colchicine, an anti-inflammatory agent with potent effects in various inflammatory diseases, might be more effective in EHOA due to the higher prominence of inflammation in this HOA subtype. As the primary goal of this study, we aimed to investigate whether colchicine could offer symptomatic relief to patients with EHOA. Additionally, as a secondary objective, we sought to determine whether colchicine therapy could significantly improve the levels of inflammation markers in these patients.

Materials and methods

Ethical statement

The ethical protocol for this study was approved by the Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (decision date: April 7, 2023; decision number: 2023/193). All procedures were conducted in compliance with the ethical standards set forth by the institutional research committee and the Helsinki Declaration and its subsequent amendments. Written informed consent was obtained from all participants.

Study design and setting

This retrospective cohort study was conducted in the Department of Rheumatology, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey, from January 2019 to December 2022.

Diagnosis of erosive hand osteoarthritis

The diagnosis of EHOA was made according to the following criteria of the American College of Rheumatology (ACR) [17]: Presence of radiological signs of EHOA, categorized as either J phase (complete disappearance of joint space in a relatively short period) or E phase (erosion of the subchondral plate concurrently or shortly after the loss of articular cartilage), observed in one or more finger joints on recently taken hand radiographs (Figure 2). Additionally, clinical findings of inflammatory osteoarthritis (i.e., pain on pressure and/or active joint swelling and/or redness and/or warmth) were identified in more than three finger joints, despite using analgesics and/or nonsteroidal anti-inflammatory drugs for over 3 months (Figure 1) [18].

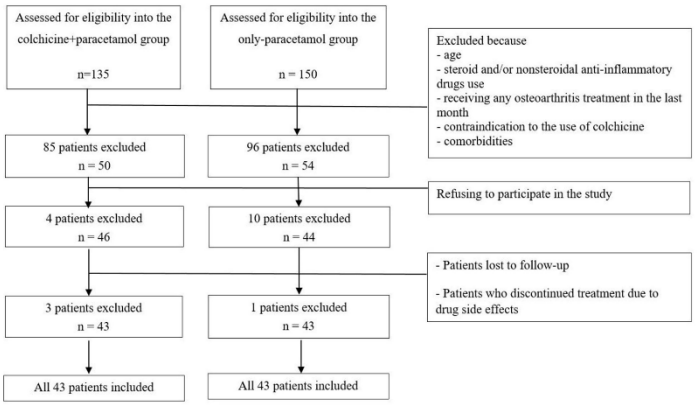
Administration of colchicine and standard treatment approach

At our center, patients with EHOA receive comprehensive information about the disease, established management approaches, and potential treatment side effects. Despite the lack of compelling evidence for the efficacy of colchicine, based on our clinical observations, we offer colchicine therapy to patients with EHOA. Before commencing treatment, we explicitly inform the patients that colchicine treatment for EHOA is a management approach not yet fully supported by scientific data, but we have observed significant improvements among recipients. Those who agreed to colchicine treatment and had no contraindications received standardized colchicine therapy and other standard treatments. The colchicine group was administered the following treatment: colchicine 2 × 0.5 mg (1 mg) and paracetamol 3 × 500 mg (1.5 gr) daily. Patients receiving colchicine were designated as the colchicine group, while those receiving paracetamol alone were labeled as the standard therapy group. After receiving the intended interventions for three months (12 weeks), both groups were examined for this study.

Study population

The patients' follow-up files were examined to identify the study groups when conducting the present study. A total of 43 EHOA patients undergoing colchicine + paracetamol treatment, who met the inclusion criteria, were included. For the control group, we randomly selected 43 EHOA patients matched for age and sex, receiving only paracetamol treatment. The inclusion criteria for the study were as follows: age between 40–80 years, diagnosed with EHOA based on the ACR criteria, a history of hand pain for at least 6 months, experiencing pain for more than half of the prior 90 days, and having a VAS pain score greater than 40 mm for hand pain within the last 48 hours [2]. Exclusion criteria included: being diagnosed with any chronic comorbidity (diabetes, hypertension, and disorders of cardiovascular, nervous, pulmonary, renal, hepatic, endocrine, or gastrointestinal systems), having any other concomitant inflammatory rheumatic disease (including gout and calcium pyrophosphate arthritis), pregnancy or breastfeeding, body mass index <20 kg/m^2 or >35 kg/m^2, use of steroid and/or immunosuppressive therapy within the prior month, receiving any osteoarthritis treatment, including physiotherapy and new hand splint(s) in the prior month, documented or suspected allergy to colchicine, failure to provide informed consent, and any drug or device use in the past 30 days related to any other research. Additionally, we excluded patients with the following laboratory values: eGFR <50 mL/min/1.73m^2, hemoglobin ≤10 g/dL, leukocyte count ≤3.5 × 10^9/L, neutrophil count ≤1.5 × 10^9/L, platelet count ≤100 × 10^9/L, and detection of >2 times the upper reference limit for alanine aminotransferase or aspartate aminotransferase [2]. Finally, any patients who refused participation or withdrew from the study, those who discontinued treatment due to side effects (paracetamol and/or colchicine), and those who had not attended control visits for at least 3 months were also excluded from the analyses. The flow diagram of the study is presented in Figure 3. We evaluated both groups 3 months after the intervention, as has been done in most previous studies [2,12,16].

Figure 3: Flowchart of the study



Data collection and instruments

Sociodemographic data, including age, sex, smoking, and alcohol use status of the participants, were recorded. From the laboratory results routinely studied in the management of patients with osteoarthritis (assessed at baseline and 3 months after treatment), we documented the following from the digital records: hemogram parameters, including hemoglobin, hematocrit, mean corpuscular volume (MCV), absolute leukocyte, neutrophil, lymphocyte, monocyte, and platelet counts, as well as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Additionally, inflammation-related indices, such as neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index (SII), and pan-immune-inflammation value (PIIV), were calculated using hemogram parameters at baseline and 3 months after treatment.

SII was calculated using the following formula: SII (× 10^3) = Absolute neutrophil count (× 10^3) × Absolute platelet count (× 10^3) / Absolute lymphocyte count (× 10^3) [19]. PIIV was calculated with the following formula: PIIV (× 10^6) = Absolute neutrophil count (× 10^3) × Absolute monocyte count (× 10^3) × Absolute platelet count (× 10^3) / Absolute lymphocyte count (× 10^3) [20].

The changes in laboratory parameters and results (amount of change) from baseline to 3 months after treatment were also included in the study as separate variables.

At baseline, the patients were asked about the duration of their osteoarthritis symptoms. Clinical measures, such as the visual analog scale (VAS) scores for pain (ranging from 0 to 100 mm) and Australian Canadian Osteoarthritis Hand Index (AUSCAN) questionnaire scores, were applied and recorded at baseline and at 3 months after treatment. The AUSCAN questionnaire was used to assess pain, stiffness, and hand function, as previously described [21]. Briefly, the AUSCAN pain score consists of five questions, each scored between 0–4, resulting in a final score between 0–20, with higher scores indicating more severe pain. The AUSCAN stiffness score consists of one question, scored between 0–4, resulting in a score between 0-4, with higher scores indicating more severe stiffness. The AUSCAN function score consists of nine questions, and each question is scored between 0–4, yielding a total function score between 0–36, with higher scores indicating worse function. The overall AUSCAN total score was obtained by summing all AUSCAN domain scores (ranging from 0 to 60). The study also examined the changes from baseline to 3 months for all scores (VAS and all AUSCAN subscores).

Laboratory analysis

The blood test-related quantitative results mentioned above were obtained from laboratory parameters routinely studied in osteoarthritis patients. No additional blood samples were drawn from the patients, and no extra laboratory work was conducted for this study. Blood samples were collected from the antecubital vein. All measurements were performed in the Clinical Biochemistry Laboratory of Afyonkarahisar Health Sciences University Hospital using routine calibrated devices and following the manufacturer's recommendations and international standards.

Efforts to address potential sources of bias

To enhance the validity and reliability of our study, we implemented several measures to address potential sources of bias. Standardized treatment protocols were employed to minimize treatment-related bias, with both paracetamol and colchicine administered to their respective groups at standardized dosages. This approach aimed to reduce variability in treatment responses and increase the study's internal validity. Additionally, we assessed demographic and clinical data, including age, sex, disease duration, and osteoarthritis severity, to control for potential confounding variables. During the statistical analysis, these baseline characteristics were considered to adjust for their potential effects on the study outcomes.

Statistical analysis

All analyses were conducted using IBM SPSS v25.0 (IBM, NY, USA), with a significance threshold set at $P<0.05$. The normality of distribution was assessed using the Shapiro-Wilk test. Continuous variables are presented as mean (standard deviation) or median (1st quartile - 3rd quartile) based on the normality of distribution. Categorical variables were reported as absolute and relative frequencies. For normally distributed variables, the Student's t-test was employed. Non-normally distributed variables were analyzed using the Mann-Whitney U test. Categorical variables were analyzed using chi-square tests (Fisher's exact and Fisher-Freeman-Halton tests when appropriate). Repeated measurements of normally distributed variables were analyzed with two-way repeated measures analysis of variance (ANOVA). On the other hand, repeated measurements of non-normally distributed variables were analyzed using the Wilcoxon Signed Ranks test. To compare between groups, the Mann-Whitney U test was used to compare the amount of difference between measurements.

Based on the effect size (0.666) reported in the study by Richette et al. [22], a sample size of 37 participants for each group (74 in total) was determined to achieve 80% power with a two-tailed 0.05 threshold for significance. The sample size calculation was performed using PASS's two-sample t-test power analysis function (Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com).

Results

The mean age of the standard therapy group was 64.79 (7.20) years, while the mean age in the colchicine group was 65.72 (7.25) years ($P=0.552$). Most patients in both groups were female, and the sex distribution was similar (76.74% vs. 79.07%; $P=1.000$). The baseline sociodemographic characteristics of the groups were similar, as summarized in Table 1.

Table 1: Summary of sociodemographic features with regard to treatment groups.

	Treatment		
	Paracetamol (n=43)	**Colchicine + Paracetamol (n=43)**	***P*-value**
Age, years	64.79 (7.20)	65.72 (7.25)	0.552
Sex			
Female	33 (76.74%)	34 (79.07%)	1.000
Male	10 (23.26%)	9 (20.93%)	
Smoking			
Yes	7 (16.28%)	3 (6.98%)	0.313
No	36 (83.72%)	40 (93.02%)	
Alcohol use			
Yes	3 (6.98%)	2 (4.65%)	1.000
No	40 (93.02%)	41 (95.35%)	

Data are given as mean (standard deviation and frequency (percentage) for categorical variables.

Table 2: Summary of laboratory measurements with regard to treatment groups.

	Treatment		
	Paracetamol (n=43)	**Colchicine + Paracetamol (n=43)**	***P*-value**
Hemoglobin, g/dL	13.20 (1.70)	13.76 (1.70)	0.127
Hematocrit, %	40.67 (4.73)	42.42 (4.74)	0.091
MCV, fl	85.0 (83.4 - 89.1)	88.9 (85.4 - 92.0)	**0.005**
Leukocyte (x10^3)			
Baseline	7.56 (6.23 - 8.90)	7.27 (5.83 - 8.91)	0.479
3rd month	7.20 (6.10 - 8.46)	6.82 (5.50 - 8.39)	0.310
***P* (within groups)**	0.717	0.187	
Change (1)	-0.04 (-0.95 - 0.66)	-0.56 (-1.77 - 1.38)	0.424
Neutrophil (x10^3)			
Baseline	4.56 (3.80 - 5.60)	4.07 (3.20 - 5.30)	0.115
3rd month	4.43 (3.60 - 5.40)	3.61 (3.10 - 4.98)	0.179
***P* (within groups)**	0.174	0.163	
Change (1)	-0.20 (-1.34 - 0.55)	-0.66 (-1.88 - 1.00)	0.843
Lymphocyte (x10^3)			
Baseline	2.15 (1.85 - 2.53)	2.27 (1.89 - 2.56)	0.487
3rd month	2.10 (1.83 - 2.50)	2.13 (1.64 - 2.58)	0.829
***P* (within groups)**	0.735	0.668	
Change (1)	0.05 (-0.50 - 0.21)	-0.12 (-0.69 - 0.30)	0.843
Monocyte (x10^3)			
Baseline	0.57 (0.33 - 0.68)	0.53 (0.42 - 0.64)	0.921
3rd month	0.55 (0.40 - 0.70)	0.46 (0.37 - 0.69)	0.442
***P* (within groups)**	0.305	0.582	
Change (1)	0.05 (-0.10 - 0.21)	-0.04 (-0.18 - 0.23)	0.204
Platelet (x10^3)			
Baseline	247 (201 - 335)	264 (215 - 315)	0.644
3rd month	250 (174 - 307)	239 (204 - 281)	0.962
***P* (within groups)**	0.447	**0.046**	
Change (1)	-2 (-38 - 21)	-31 (-63 - 18)	0.106
NLR			
Baseline	2.12 (1.80 - 2.47)	1.69 (1.25 - 2.49)	0.053
3rd month	1.95 (1.61 - 2.45)	1.66 (1.28 - 2.90)	0.179
***P* (within groups)**	0.305	0.469	
Change (1)	-0.14 (-0.71 - 0.36)	-0.25 (-0.81 - 0.65)	0.819
MLR			
Baseline	0.26 (0.17 - 0.32)	0.23 (0.18 - 0.32)	0.945
3rd month	0.25 (0.17 - 0.37)	0.22 (0.17 - 0.39)	0.680
***P* (within groups)**	0.274	0.875	
Change (1)	0.03 (-0.06 - 0.10)	0.00 (-0.12 - 0.10)	0.370
PLR			
Baseline	102.08 (87.57 - 144.39)	119.17 (96.51 - 141.53)	0.506
3rd month	112.31 (80.56 - 140.00)	117.15 (95.54 - 158.54)	0.554
***P* (within groups)**	0.754	0.952	
Change (1)	-3.53 (-20.13 - 24.97)	-1.79 (-34.20 - 33.49)	0.826
SII (x10^3)			
Baseline	502.02 (341.74 - 819.06)	487.35 (289.76 - 693.28)	0.427
3rd month	467.33 (331.29 - 706.48)	426.52 (277.72 - 709.30)	0.409
***P* (within groups)**	0.218	0.218	
Change (1)	-36.28 (-243.43 - 92.58)	-96.19 (-379.52 - 142.22)	0.566
PIIV (x10^6)			
Baseline	302.95 (110.55 - 557.84)	243.91 (135.44 - 414.88)	0.660
3rd month	287.41 (132.51 - 419.23)	187.74 (123.73 - 441.95)	0.409
***P* (within groups)**	0.413	0.316	
Change (1)	-19.45 (-175.35 - 88.49)	-29.80 (-263.90 - 152.04)	0.758
ESR, mm/h			
Baseline	30.74 (11.10	31.02 (12.74	0.914
3rd month	32.67 (11.00	19.88 (8.52	**<0.001**
***P* (within groups)**	0.113	**<0.001**	
Change (1)	1.93 (5.83	-11.14 (9.54	**<0.001**
CRP, mg/L			
Baseline	5.1 (2.7 - 6.35)	5.8 (3.0 - 9.3)	0.183
3rd month	5.4 (3.7 - 7.7)	2.1 (1.2 - 4.4)	**<0.001**
***P* (within groups)**	**0.022**	**<0.001**	
Change (1)	0.2 (-0.3 - 1.03)	-2.93 (-5.0 - -0.9)	**<0.001**

Data are given as mean (standard deviation or median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution. (1) Difference between 3rd month and baseline, negative values represent a decrease, and positive values represent an increase. CRP: C-reactive protein, ESR: Eritrosit sedimentation rate, MCV: Mean corpuscular volume, MLR: Monocyte-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, PIIV: Pan-immune-inflammation value, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index

Standard therapy recipients' baseline MCV was significantly lower than that of colchicine recipients (P=0.005). In the third month, ESR and CRP levels in the colchicine group were significantly lower compared to the standard therapy group (Figure 4). Moreover, the reductions in ESR and CRP levels from baseline were significantly greater in the colchicine group than in the standard therapy group (P<0.001 for all). The colchicine group showed significant decreases in platelet count (P=0.046), ESR level (P<0.001), and CRP level (P<0.001) from baseline to 3 months. Interestingly, the standard therapy group demonstrated a significant increase in CRP values at 3 months compared to baseline (P=0.022) (Table 2).

At 3 months, the VAS and Australian/Canadian Osteoarthritis Hand Index (AUSCAN) scores (pain, stiffness, function, and total score) of the colchicine group were significantly lower compared to the standard therapy group (P<0.001 for all) (Figure 5). The baseline-to-3rd-month decreases in VAS and AUSCAN scores were significant for both treatment groups (P<0.001 for all). However, the amount of decrease in these scores (from baseline to 3 months) was significantly greater in colchicine recipients compared to standard therapy recipients (P<0.001 for all) (Table 3).

Figure 4: Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) with regard to treatment groups *P<0.05, ** P<0.001, # P>0.05

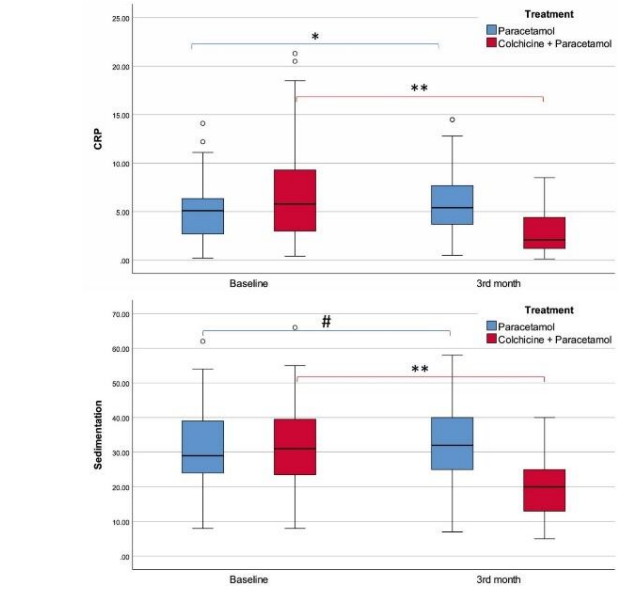


Figure 5: Visual analog scale (VAS) pain score and Australian Canadian Osteoarthritis Hand Index (AUSCAN) total score with regard to treatment groups ** P<0.001, *** P<0.0001

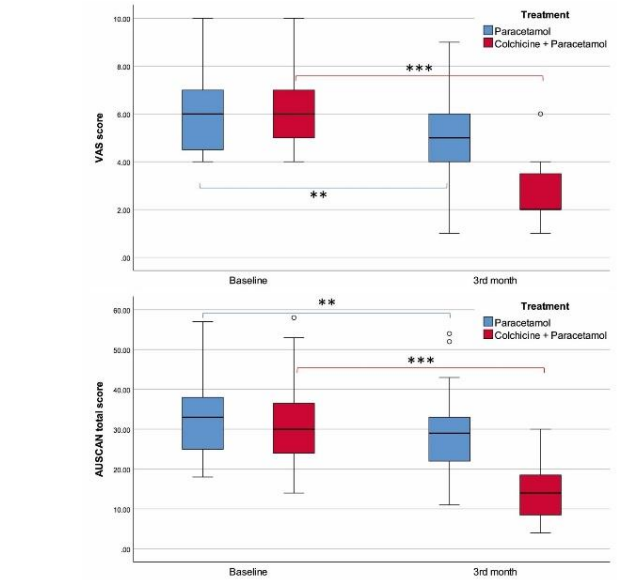


Table 3: Summary of symptomatic features and scale scores with regard to treatment groups

	Treatment		
	Paracetamol (n=43)	**Colchicine + Paracetamol (n=43)**	***P*-value**
Duration of symptoms, months	30 (15 - 60)	36 (20 - 62)	0.320
Visual analog scale score			
Baseline	6 (4.5 - 7)	6 (5 - 7)	0.338
3rd month	5 (4 - 6)	2 (2 - 3.5)	**<0.001**
***P* (within groups)**	**<0.001**	**<0.001**	
Change [(1)]	-1 (-1 - 0)	-4 (-5 - -2)	**<0.001**
AUSCAN pain score			
Baseline	12 (10 - 14)	12 (9 - 14)	0.855
3rd month	11 (8 - 12)	4 (3 - 6)	**<0.001**
***P* (within groups)**	**<0.001**	**<0.001**	
Change [(1)]	-1 (-2 - -1)	-8 (-9 - -6)	**<0.001**
AUSCAN stiffness score			
Baseline	2 (2 - 3)	2 (1 - 3)	0.245
3rd month	2 (1 - 3)	1 (0 - 1)	**<0.001**
***P* (within groups)**	**0.047**	**<0.001**	
Change [(1)]	0 (-1 - 0)	-1 (-2 - -1)	**<0.001**
AUSCAN function score			
Baseline	19 (13 - 22)	16 (12 - 20)	0.196
3rd month	17 (11 - 20)	8 (5 - 11)	**<0.001**
***P* (within groups)**	**<0.001**	**<0.001**	
Change [(1)]	-2 (-3 - -1)	-7 (-10 - -5)	**<0.001**
AUSCAN total score			
Baseline	33 (25 - 38)	30 (24 - 36.5)	0.294
3rd month	29 (22 - 33)	14 (8.5 - 18.5)	**<0.001**
***P* (within groups)**	**<0.001**	**<0.001**	
Change [(1)]	-4 (-5 - -2)	-17 (-20 - -13)	**<0.001**

Data are given as median (1st quartile - 3rd quartile) for continuous variables according to normality of distribution. (1) Difference between 3rd month and baseline, negative values represent a decrease, and positive values represent an increase. AUSCAN: The Australian Canadian Osteoarthritis Hand Index.

Discussion

This retrospective cohort study utilized a prospective collection of follow-up data from patients with EHOA. The study shows that both treatments, paracetamol + colchicine and paracetamol alone, led to significant improvements in VAS and AUSCAN scores (including pain, stiffness, function, and total score) among patients with EHOA. However, the colchicine group showed greater improvements in VAS and AUSCAN scores, as evidenced by direct comparisons at 3 months and the change in scores. Additionally, recipients of colchicine also demonstrated significant decreases in CRP and ESR levels, with significantly lower ESR and CRP levels at 3 months compared to the standard therapy group.

The main challenge in developing treatments that can effectively control the initiation and progression of EHOA is the lack of understanding of the underlying pathological processes [5]. While analgesics provide temporary and partial relief for EHOA symptoms, no pharmacotherapeutics currently can truly treat EHOA [2]. Given that osteoarthritis is common in old age and the proportion of elderly individuals in the population is increasing, there is an evident need for effective treatments [3,5]. Colchicine is well-established as an effective drug for reducing joint pain and swelling in gouty arthritis and other diseases, but positive results regarding its efficacy in osteoarthritis have not been reported [2]. Although there is a considerable number of studies on the use of colchicine in knee osteoarthritis, research on its efficacy in treating HOA is quite limited. In the present study, a 12-week treatment with 1.5 grams of paracetamol plus 1 mg of colchicine daily resulted in greater reductions in VAS scores and AUSCAN outcomes (pain, stiffness, function, and total score) compared to just 1.5 grams of paracetamol daily. Furthermore, while the scores of the two groups were similar at baseline, the colchicine group demonstrated significantly lower scores after 12 weeks of treatment.

Davis et al. [2] conducted a randomized, double-blind, placebo-controlled clinical trial with the hypothesis that

colchicine might be effective in HOA based on the idea that inflammatory osteoarthritis was more common in HOA than knee osteoarthritis. To our knowledge, this was the first study to investigate the efficacy of colchicine in HOA. The researchers reported that colchicine (1 mg daily for 12 weeks) was ineffective in reducing pain, the number of tender and swollen joints, ultrasound synovitis grade, and scores from the Michigan Hand Questionnaire, or increasing grip strength in symptomatic HOA. Therefore, the results did not support the use of colchicine in HOA. However, it should be noted that approximately 60% of the subjects in this study [2] had EHOA, while almost half of the patients did not have EHOA, which might have confounded findings and masked potential benefits exclusive to patients with EHOA. Plotz et al. [23], in their response to the study mentioned above, emphasized that Davis et al. did not require the presence of erosive, tender, swollen, or painful joints when including patients, which could have limited the number of subjects with active disease since these are well-established indicators of active inflammation.

Additionally, they did not assess Doppler signals when selecting subjects. Therefore, the study population did not consist of a sufficient number of patients with active inflammation, significantly limiting the accuracy of the evaluation of treatment. Large studies testing anti-inflammatory therapy must strive to include patients with inflammation, perhaps exclusively those with active inflammation, as the exposure (treatment) would be expected to demonstrate its effects mainly in these patient subsets. Secondly, the researchers did not consider pre-existing analgesic medications or provide any relevant data in this context. Thirdly, while colchicine is expected to decrease CRP as it suppresses inflammation, the authors did not discuss the possible reasons for the alarming increase in CRP levels after treatment [23]. We agree with the objections put forth by Plotz et al. [23] because it is evident that EHOA differs from non-EHOA in terms of both clinical severity and response to treatment. In a recent study, a group receiving 0.5 mg of colchicine twice daily for 12 weeks was compared to a placebo group for changes in target finger pain from baseline to week 12. The study reported that treatment with colchicine did not effectively reduce pain or improve AUSCAN scores in people with painful hand osteoarthritis and caused more side effects. However, the study population did not solely include EHOA cases [16]. We think it would be a better choice to investigate the efficacy of colchicine in a study population including only patients with EHOA, as was the case with the current study.

Studies on the use of colchicine in the treatment of knee osteoarthritis offer conflicting results. In one study of patients with knee osteoarthritis, treatment with colchicine (in addition to the standard therapy) resulted in greater improvement in patient- and physician-assessed outcomes at 3 months after treatment initiation [12]. A systematic review on colchicine in knee osteoarthritis stated that colchicine appears to be an effective and safe alternative for treating knee osteoarthritis, as evidenced by lower pain and improved functionality [13]. Similarly, some other studies have claimed that colchicine improves symptoms in treating knee osteoarthritis [24–26].

However, in contrast, Leung et al. [14] reported that colchicine (0.5 mg oral, twice daily) did not reduce symptoms of knee osteoarthritis, as measured by the Western Ontario and McMaster Universities Osteoarthritis Index score during a 16-week study period. Another study compared the efficacy of physiotherapy and colchicine in patients with knee osteoarthritis and found that physical therapy was more effective than colchicine in reducing symptoms. Additionally, there were no significant differences in ultrasound-determined parameters at the end of the 16 weeks [15].

ESR and CRP values can detect inflammation, but these tests are not specific to osteoarthritis [26]. CRP is an inflammatory marker produced in the liver and released into the blood as a result of the stimulation of cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α [28–30]. Colchicine can inhibit CRP production, but corticosteroids and other anti-inflammatory or immunosuppressive drugs cannot [28]. ESR is a common hematology test that can increase in the presence of inflammatory activity due to various disorders, including autoimmune diseases, acute inflammatory pathologies, infections, tumors, rheumatological diseases, and conditions causing increased physiological stress (such as pregnancy) [27–31]. While ESR and CRP levels are expected to increase in osteoarthritis, the effect of colchicine on the ESR and CRP levels of patients with EHOA is unclear [27].

In the present study, the combined use of colchicine and paracetamol resulted in a significant reduction in both ESR and CRP after 3 months, but no significant reduction was observed in the paracetamol-only group. Furthermore, while the baseline CRP and ESR levels were similar in both groups, the 3rd-month results showed that colchicine recipients' ESR and CRP levels were significantly lower compared to the standard therapy group. This result was further reinforced by the significantly greater decrease in ESR and CRP values in the colchicine group. Intriguingly, there was a significant increase in the CRP levels of the standard therapy group after 3 months of treatment, lending further credibility to the utility of colchicine and demonstrating that paracetamol alone was insufficient to prevent hyperinflammation.

In one study, it was reported that colchicine (0.5 mg orally twice a day) decreased inflammation markers, including CRP and bone turnover biomarkers, known to be associated with osteoarthritis severity and the risk of progression, but these differences were not significant [14]. Conversely, the study by Davis et al. [2] showed that 12 weeks of colchicine treatment did not significantly affect CRP levels in patients with HOA compared to placebo.

The fact that HOA tends to be predominantly symmetrical has an erosive subtype, and occurs in non-weight-bearing joints suggests that it may be affected to a greater degree by the systemic effects of osteoarthritis relative to hip and knee osteoarthritis [32,33]. Despite these data, most studies examining the response of HOA to therapeutic agents targeting specific inflammatory mediators have failed to reach their primary endpoints [23]. These 'unsuccessful' anti-inflammatory agents include hydroxychloroquine [34], lebrikizumab [35], adalimumab [36], etanercept [37], and tocilizumab [22].

On the other hand, the HOPE study stated that 10 mg of prednisolone for 6 weeks was effective and safe in treating patients with painful HOA and signs of inflammation [38].

Although these results suggest a feasible short-term treatment option for patients with HOA exacerbation, it is clear that there is a need for alternative treatment options due to the adverse effects of steroids [39]. Moreover, the possible differences in the pathological processes and inflammatory burdens of HOA subtypes necessitate the differentiation of management strategies. However, no studies have investigated the efficacy of colchicine in patients with EHOA. A recently published review reported that current evidence did not suggest a benefit for colchicine in reducing pain and improving physical function in patients with hand/knee osteoarthritis, but the authors also suggested that future studies investigating colchicine should focus on different osteoarthritis subtypes [40].

In our clinical experience, we have observed that colchicine significantly improves EHOA patients. Furthermore, the significant decrease in ESR and CRP levels supported the anti-inflammatory effect of colchicine. We hope our results will sufficiently trigger further comprehensive studies investigating the efficacy of daily treatment with colchicine (2 × 0.5 mg) + paracetamol (3 × 500 mg) in patients with EHOA.

Limitations

To the best of our knowledge, this is the first study investigating the efficacy of colchicine in patients with EHOA. Our results illustrate the utility of colchicine in patients with EHOA, as demonstrated by improvements in pain and AUSCAN scores. However, it should be noted that the study has some limitations. Primarily, it is a retrospective cohort study conducted at a center that offers colchicine therapy to patients. Although including only those with EHOA was necessary to enable reliable comparisons between treatments, the fact that it is a single-centered study with a relatively small sample size of EHOA patients limits the generalizability of its results. The efficacy of colchicine was evaluated using pain and AUSCAN scores, but further objective tools such as ultrasonographic examination, grip strength, and magnetic resonance imaging were not employed, which should be the focus of future prospectively-planned studies.

The treatments were administered for 12 weeks; only patients who attended follow-up studies during therapy were included. Therefore, those who did not benefit would have had a greater likelihood of being lost to follow-up, potentially skewing the results towards patients who benefitted from colchicine therapy. To prevent such confounding, future studies should employ ‘intention-to-treat’ analyses. The short follow-up period also limits the evaluation of long-term effects and potential side effects. Thus, more extended follow-up periods are necessary to assess the treatment’s lasting impact and safety profile.

Conclusions

In conclusion, the concomitant use of colchicine and paracetamol for 12 weeks appears to lead to greater improvements in CRP and ESR levels, VAS score, and AUSCAN scores compared to paracetamol alone in patients with EHOA. Despite the need for further studies considering the limitations of the present study, colchicine shows promise as an effective therapeutic agent in the treatment of EHOA.

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