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RESEARCH ARTICLE

The Effects of Colchicine Treatment on Cardiac and Inflammatory Markers in COVID-19 Patients Followed Up in Intensive Care Unit

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ABSTRACT

Objective: It has been stated that colchicine can reduce the cytokine storm and inflammation in cardiac myocytes during COVID-19 infection. This study aims to investigate the effect of colchicine treatment on cardiac and inflammatory markers in COVID-19 patients followed in the intensive care Unit (ICU) of a tertiary center.

Materials and Methods: Patients followed up in the ICU with the diagnosis of COVID-19 between April 2020 and June 2020 were evaluated retrospectively. Patients who received standard treatment in moderate-to-severe COVID-19 patients were analyzed by classifying them as the control group and patients who were added to the standard treatment within the first 48 h as the colchicine group.

Results: A total of 79 patients, 39 in the colchicine group and 40 in the control group, were included in the study. Demographic data and the presence of comorbid disease were similar between groups. The mean length of stay in the ICU was 19.4±8 days in the colchicine group and 14.7±7 days in the control group. The length of stay in the ICU was found to be significantly higher in the colchicine group (p=0.017). There was no significant difference between the groups in terms of C-reactive protein, Interleukin-6, troponin T and D-dimer levels, and 28-day mortality (94.9% vs. 95%, p>0.05).

Conclusion: Adding oral colchicine to the standard treatment within the first 48 h after hospitalization in moderate-to-severe COVID-19 patients followed in the ICU did not improve the clinical status of the patients. It did not reduce cardiac and inflammatory markers and mortality rates.

Keywords: Colchicine, COVID-19, CRP, D-dimer, inflammation, troponin T

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INTRODUCTION

COVID-19 disease caused by SARS-CoV-2 is a severe cause of morbidity and mortality affecting millions of people worldwide. COVID-19 can progress in various clinical forms, from asymptomatic or mild clinical forms to severe bilateral pneumonia and death.[1] After infection of the cell with SARS-CoV-2 and the first stage of viral replication, many patients develop an exaggerated inflammatory response called a cytokine storm.[2] It has been reported that cytokine storms can progress to cardiovascular disorders such as pulmonary edema, acute respiratory distress syndrome, endothelial damage and thrombosis, and progressive multi-organ failure.[3]

Colchicine is a widely used, inexpensive anti-inflammatory drug for patients with gout, rheumatic diseases, and pericarditis. In addition, it has been reported that colchicine may have a potential role in patients with coronary disease.[4] Although cytokine storms of COVID-19 are generally seen in the elderly and patients with comorbid conditions such as hypertension, diabetes, obesity, and smoking, it has been reported that colchicine can reduce the cytokine storm seen during COVID-19 infection.[5] Colchicine has also reduced inflammation in cardiac myocytes in some COVID-19 patients with myopathy.[6] It has been thought that colchicine, readily available and inexpensive worldwide, can be used as a potential agent for treating COVID-19.[7]

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This study aims to investigate the effect of colchicine use on cardiac and inflammatory markers in COVID-19 patients followed up and treated in the intensive care unit (ICU) of a tertiary center.

MATERIALS and METHODS

This retrospective observational study was started after receiving approval from the local clinical research ethics committee (date: 22.04.2021, number:117). The principles of the Declaration of Helsinki were used to conduct the study. The patients were followed up and treated in the 14-bed capacity COVID-19 ICU on the relevant dates by the Anesthesiology and Reanimation Clinic at the University of Health Sciences, Istanbul Kanuni Sultan Süleyman Training and Research Hospital.

COVID-19-positive patients who were followed up and treated in the ICU between April 2020 and June 2020 were evaluated retrospectively. Patients with severe renal impairment (glomerular filtration rate <30 mL/min/1.73 m^2), with a history of active hepatitis, cirrhosis, or severe liver failure, prior colchicine use, and immunosuppressive patients were excluded from the study. Inclusion criteria; 18 years of age and older, COVID-19 infection confirmed by polymerase chain reaction (PCR) in nasal swab sample or negative PCR test but thoracic tomography suggestive of COVID-19, admitted to the ICU within 72 h after the diagnosis of COVID-19, clinical and laboratory were determined as moderate-severe patients with no deficiency in their results. Moderate-to-severe COVID-19 infection was defined as patients who received high-level nasal oxygen therapy, and invasive or non-invasive mechanical ventilation therapy. During the COVID-19 pandemic, Anesthesiology and Reanimation specialists and Intensive care specialists treated patients in our ICU using the protocols the Ministry of Health recommended. Patients who added 2 ×1 0.5 g of oral colchicine for at least 5 days within 48 h of hospitalization to standard COVID-19 treatment were classified as the colchicine group. Patients who received standard COVID-19 treatment were determined as the control group. Colchicine treatment was started in line with the clinical condition of the patients, the availability of colchicine in the hospital, and the preference of the clinicians working in the ICU.

Demographic data of the patients, presence of comorbid disease, length of stay in the ICU, cardiac and inflammatory markers C-reactive protein (CRP, reference range <5 mg/L), ferritin (30–400 ng/mL), Interleukin-6 (IL-6, 0–7 pg/mL), troponin T (0–0.014 ng/mL), and D-dimer (0–0.55 ng/mL) levels from the morning blood samples taken routinely for 5 days after COVID-19 treatment and 28-day mortality were recorded over the hospital information system.

The G*Power 3.1 program was used to determine the sample size. The primary efficacy analysis was performed on an intention-to-treat basis. Sample size has been calculated using a significance level of 0.05, effect size=0.6, and 80% power for the event of an average deterioration/improvement of 1 point in favor of the intervention group. The estimated sample size was determined as 72 people, with 36 people in each group.

Statistical Analysis

SPSS 29.0 (SPSS Inc., Chicago, USA) program was used to analyze the data. Descriptive data are expressed as the number of patients, percentage, mean, and standard deviation. The conformity of the variables to the normal distribution was evaluated analytically (Shapiro–Wilks test) and visually (histogram). The Chi-square test was used to assess qualitative data, and the matched sample t-test was used for repeated cardiac and inflammatory markers measurements. The Mann–Whitney U test analyzed cardiac and inflammatory markers between groups. The statistical significance limit was accepted as $p<0.05$.

RESULTS

A total of 79 patients, 39 in the colchicine group and 40 in the control group, were included in the study. In the colchicine group, 62.5% (n=25) of the patients were male, and the mean age was 65.6±13, while in the control group, 61.5% of the patients (n=24) were male, and the mean age was 65.1±11 years. The comorbid disease was present in 85% (n=34) of the colchicine group and 79.5% (n=31) of the patients in the control group. While the mean duration of stay in the ICU was 19.4±8 days in the colchicine group, it was 14.7±7 days in the control group. While the 28-day mortality of the patients was 94.9% (n=37) in the colchicine group, it was 95% (n=38) in the control group. There was no significant difference between the groups regarding age, gender, comorbid disease, and mortality (p=0.527, p=0.930, p=0.521, and p=0.521, respectively). However, the length of stay in the ICU was significantly higher in the colchicine group (p=0.017) (Table 1).

The values of CRP according to time and groups are shown in Figure 1. CRP values in the colchicine group, except for the first measurement CRP values, were lower than in the control group, although they were insignificant (p>0.05). The change of troponin T according to time and groups is shown in Figure 2. Although troponin T values were lower in the colchicine group than in the control group, no significant

Table 1. Demographic data of patients, distribution of some clinical characteristics

	Colchicine group (n=39)		Control group (n=40)		p
	n	%	n	%	
Age (years)	65.6±13.3		65.1±11.8		0.527
Gender					
Female	15	38.5	15	37.5	0.930
Male	24	61.5	25	62.5	
Comorbidity	31	79.5	34	85	0.521
Duration of ICU (days)	19.4±8.9		14.7±7.5		0.017
Mortality (28-day)	37	94.9	38	95	0.521

Data are given as mean±standard deviation, the number of patients (n), and percentage. ICU: Intensive care unit

difference was found (p>0.05). The measurements of IL-6 according to time and groups are shown in Figure 3. All IL-6 measurement results in the colchicine group were lower, although insignificant, than the control group (p>0.05). The variation of ferritin according to time and groups is shown in Figure 4. The groups had no significant difference regarding ferritin measurement results (p>0.05).

The measurements of the D-dimer according to time and groups are shown in Figure 5. Although D-dimer values were lower in the colchicine group than in the control group, no significant difference was observed (p>0.05) (Table 2).

DISCUSSION

Inflammatory and cardiac markers such as CRP, ferritin, troponin T and D-dimer and proinflammatory cytokines such as IL-6 have been reported to have prognostic value in evaluating the severity of the disease in COVID-19 patients.[8] A massive proinflammatory response or cytokine storm may progress to multi-organ failure in these patients. Colchicine has been used for years to treat inflammatory diseases, such as familial Mediterranean fever, Behçet's disease, gout, and pericarditis. It has been reported that colchicine gives beneficial results in conditions such as pericarditis, pneumonia, and lung involvement of unknown origin due to the Eppstein–Barr Virus, Cytomegalovirus, and influenza B viruses.[9,10] In this context, it has been suggested that colchicine, which has anti-inflammatory and antiviral properties, can treat COVID-19.

It has been reported that CRP levels increase in COVID-19 patients and correlate with the severity of the disease. Ruan et al.[11] said that the median CRP levels of survivors among patients who followed up for COVID-19 were 40 mg L^{-1}, and

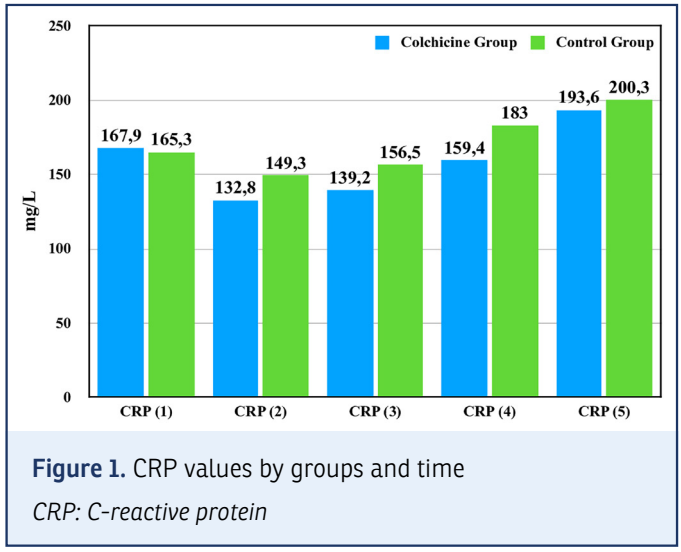

Figure 1. CRP values by groups and time

CRP: C-reactive protein

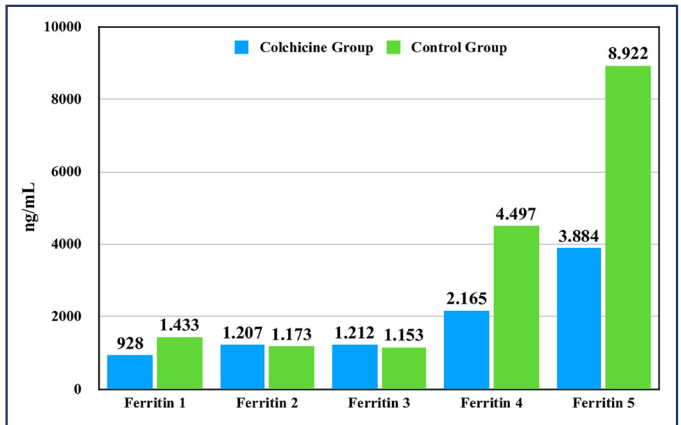

Figure 2. Ferritin values by groups and time

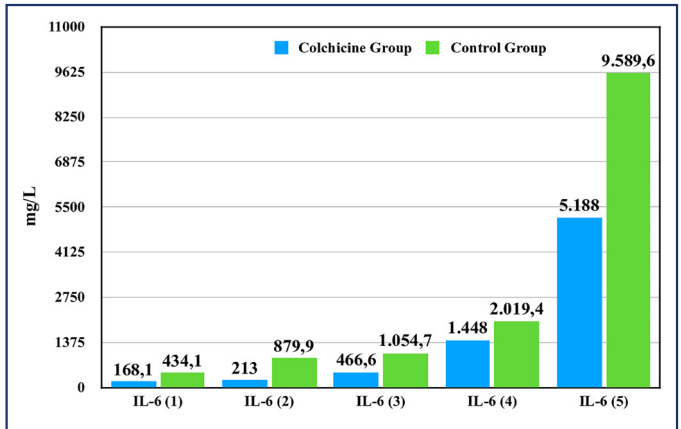

Figure 3. IL-6 values by groups and time

IL-6: Interleukin-6

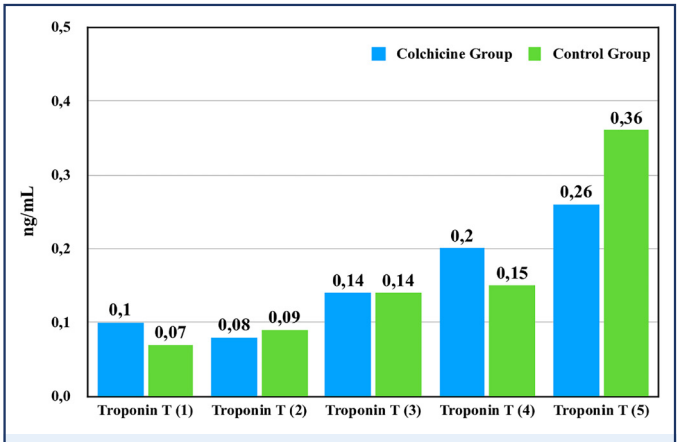

Figure 4. Troponin T values by groups and time

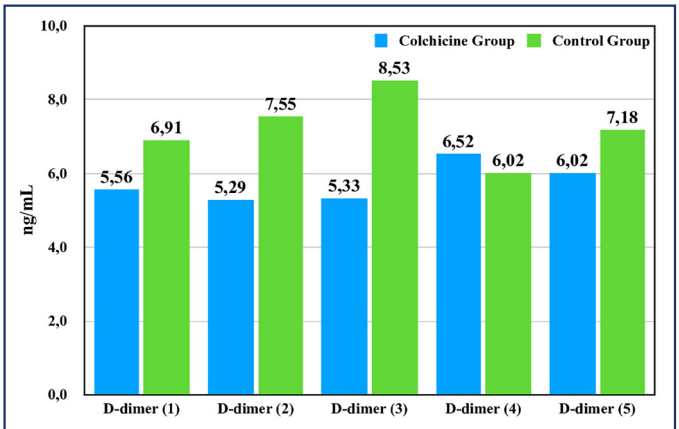

Figure 5. D-dimer values by groups and time

those who died were 125 mg L^{-1}. Another study reported that low-dose colchicine could effectively reduce high-sensitivity CRP independently of acetylsalicylic acid and atorvastatin in patients with stable coronary artery disease.[12] Sarwar et al.[13] investigated the effect of colchicine on hematological parameters in COVID-19 patients in their meta-analysis. They emphasized that colchicine can reduce CRP in moderate-to-advanced COVID-19 patients. In our study, the mean CRP values measured on the 5th day in the colchicine group were 193.6±108 (14–550), while it was 200.3±130 (2.3–506) in the control group. Our patients in both groups were in a severe COVID-19 clinic, and the high mortality rates influenced the high average CRP values. Although there was a decrease in CRP values in the colchicine group compared to the control group, no significant difference was found between the groups.

It is known that ferritin level has a diagnostic value in COVID-19 patients. It has been reported that ferritin levels may increase too much due to secondary hemophagocytic lymphohistiocytosis and cytokine storm syndrome in COVID-19 patients. It is also an indicator of poor prognosis.[14,15] Pascual-Figal et al.[7] reported that the ferritin values of colchicine added to standard treatment in COVID-19 patients who were not hospitalized in the ICU showed a decrease in ferritin values compared to the control group. Although the fifth measurement ferritin level was lower in the colchicine group than in the control group, no significant difference was found in our study.

It has been reported that IL-6 levels increase in complicated and progressing COVID-19 cases.[16] Pascual-Figal et al.[7] said that the IL-6 value in the colchicine group was lower

Table 2. Distribution of cardiac and inflammatory markers by groups and time

	Colchicine group (n=39)	Control group (n=40)	p
CRP (mg/L) (1)	167.9±95.4	165.3±97.9	0.698
CRP (mg/L) (2)	132.8±107.2	149.3±95.1	0.201
CRP (mg/L) (3)	139.2±85.8	156.5±106	0.533
CRP (mg/L) (4)	159.4±91.8	183±124	0.502
CRP (mg/L) (5)	193.6±108.9	200.3±130.2	0.879
Ferritin (ng/mL) (1)	928±954	1433±1421	0.104
Ferritin (ng/mL) (2)	1207±1471	1173±1312	0.810
Ferritin (ng/mL) (3)	1212±841	1153±1204	0.196
Ferritin (ng/mL) (4)	2165±2682	4497±10491	0.364
Ferritin (ng/mL) (5)	3884±9640	8922±14761	0.112
IL-6 (pg/mL) (1)	168±233	434±998	0.206
IL-6 (pg/mL) (2)	213±465	879±2356	0.385
IL-6 (pg/mL) (3)	466±1222	1054±2292	0.965
IL-6 (pg/mL) (4)	1448±3571	2019±5072	0.969
IL-6 (pg/mL) (5)	5188±10820	9589±17050	0.784
Troponin T (ng/mL) (1)	0.1±0.3	0.07±0.1	0.787
Troponin T (ng/mL) (2)	0.08±0.22	0.09±0.17	0.543
Troponin T (ng/mL) (3)	0.14±0.27	0.14±0.36	0.433
Troponin T (ng/mL) (4)	0.2±0.45	0.15±0.33	0.245
Troponin T (ng/mL) (5)	0.26±0.59	0.36±0.93	0.841
D-dimer (ng/mL) (1)	5.56±8.3	6.91±9.6	0.447
D-dimer (ng/mL) (2)	5.29±6.27	7.55±8.8	0.385
D-dimer (ng/mL) (3)	5.33±6.02	8.53±14	0.634
D-dimer (ng/mL) (4)	6.52±6.80	6.02±5.6	0.772
D-dimer (ng/mL) (5)	6.02±5.89	7.18±6.2	0.550

Values are the mean±standard deviation. CRP: C-reactive protein; IL-6: Interleukin-6

than in the control group, but there was no significant difference between the groups. Our study detected increased IL-6 values in the colchicine group from the first measurement. Consistent with the literature, all IL-6 sizes in the colchicine group were smaller, although not significant, than the control group.

Cardiac dysfunction and arrhythmias may be seen in COVID-19 patients due to viral myocarditis, myocardial damage due to cytokines, and exacerbation of coronary artery diseases.[8] Pascual-Figal et al.[7] reported that the troponin T value was lower in COVID-19 patients who used colchicine compared to the control group. However, there was no significant difference between the groups. In our study, the troponin T value in the fifth measurement was significantly higher than in the first in both the colchicine and control groups. Consistent with the literature, no significant difference was found, although troponin T values were lower in the colchicine group than in the control group.

Increases in D-dimer observed in COVID-19 patients were associated with disease progression and a broad spectrum of thromboembolic events such as pulmonary micro-thrombosis and deep vein thrombosis. They even disseminated intravascular coagulation (DIC).[8] Coagulation disorders and DIC increase mortality. An increase of >1 μgL^{-1} in D-dimer strongly indicates mortality.[1] Another study said the D-dimer value was higher in the colchicine group in COVID-19 patients than in the control group. However, the difference between the groups was not significant.[7] In our study, following the literature, although D-dimer measurements were lower in the colchicine group than in the control group, no significant difference was observed.

Study Limitations

The study's limitations are that it is retrospective, single-center, and the sample size is small. In addition, the patients included in the study were admitted to the ICU within 72 h after being positive for COVID-19. The exact time has not been determined.

CONCLUSION

In conclusion, adding oral colchicine to the standard treatment within the first 48 h after hospitalization in moderate-to-severe COVID-19 patients followed in the ICU did not improve the clinical status of the patients. It did not reduce cardiac and inflammatory markers and mortality rates. Multicenter prospective studies are needed to define the role of colchicine in clinical recovery in COVID-19 patients.

Disclosures

Ethics Committee Approval: The study was approved by the Kanuni Sultan Süleyman Training and Research Hospital Clinical Research Ethics Committee (No: 117, Date: 22/04/2021).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

Authorship Contributions: Concept: M.A., K.A., E.K., A.S.Ş.; Design: M.A., A.S.Ş.; Supervision: K.A., E.K., A.S.Ş.; Funding: M.A.; Materials: M.A., A.S.Ş.; Data Collection or Processing: M.A.; Analysis or Interpretation: K.A., E.K., A.S.Ş.; Literature Search: K.A., E.K., A.S.Ş.; Writing: M.A., K.A., E.K., A.S.Ş.; Critical review: K.A., E.K., A.S.Ş.

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

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