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Efficacy of colchicine treatment in COVID-19 patients: A case-control study

COVID-19 hastalarında kolşisin tedavisinin etkinliği: Bir vaka-kontrol çalışması

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Abstract

Aim: Various clinical studies have been conducted on many alternative options in treating COVID-19 since the beginning of the pandemic process. This study aimed to investigate the effectiveness of colchicine treatment in patients hospitalized in clinical wards due to COVID-19.

Methods: The study was retrospectively planned between October 2020 and October 2021. A total of 110 cases who received colchicine + standard treatment (favipiravir + corticosteroid + anticoagulant + symptomatic treatment) were included in the study group. The control group included randomly selected 220 patients who received only standard treatment. All cases' demographic characteristics, features of antibiotic and corticosteroid treatment, comorbidities, and clinical courses were recorded. Patients who received treatment for less than three days due to COVID-19, patients aged >95 years and <18 years, and those transferred to the clinical wards from the intensive care unit were excluded from the study. The groups were compared regarding treatment failure, including the number of intensive care unit admissions and mortality due to COVID-19 infection.

Results: While the mean age was 59.4 years in the study group, it was 65.0 years in the control group (p=0.001). The most common coexisting disease was hypertension (63%). There were significant differences between the groups in the proportions of antibiotic use (p=0.002) and high-dose corticosteroid use (p=0.004). The values of white blood cell count (p=0.003), urea (p=0.029), D-dimer (p=0.021), creatine kinase-myocardial band (p=0.003) and troponin (p<0.001) were statistically different. There was no difference in terms of intensive care unit admission (p=0.174), the mortality rate (p=1.000), and treatment failure (p=0.505).

Conclusions: According to the results of our study, colchicine treatment does not affect the prognosis of COVID-19 patients. There is a need for prospective studies investigating the role of colchicine treatment in COVID-19 infections.

Keywords: COVID-19 virus infection, colchicine, mortality rate, intensive care.

Öz

Amaç: Pandemi sürecinin başlangıcından bu yana COVID-19 enfeksiyonu tedavisinde birçok alternatif seçenek üzerinde çeşitli klinik çalışmalar yapılmıştır. Çalışmanın amacı, COVID-19 nedeniyle hastaneye yatırılan ve yataklı serviste takip edilen hastalarda kolşisin tedavisinin etkinliğini araştırmaktır.

Yöntemler: Çalışma Ekim 2020 – Ekim 2021 tarihleri arasında retrospektif olarak planlandı. Çalışma grubuna kolşisin + standart tedavi (favipiravir + kortikosteroid + antikoagülan + semptomatik tedavi) alan 110 vaka, kontrol grubuna ise sadece standart tedavi alan 220 vaka rastgele dahil edildi. Tüm olguların demografik özellikleri, antibiyotik ve kortikosteroid kullanımı, komorbidite durumları ve klinik seyirleri kaydedildi. COVID-19 nedeniyle üç günden az tedavi görenler, 95 yaş üstü ve 18 yaş altı hastalar ve yoğun bakım ünitesinden servise alınan hastalar çalışma dışı bırakıldı. Gruplar yoğun bakım ünitesine yatış ve mortalite olarak tanımlanan COVID-19 enfeksiyonu tedavi başarısızlığı açısından karşılaştırıldı.

Bulgular: Yaş ortalaması olgu grubunda 59,4 yıl ve kontrol grubunda 65,0 yıl idi (p=0,001). En sık görülen komorbidite durumu hipertansiyon (%63) idi. İki grup arasında antibiyotik (p=0,002) ve yüksek doz kortikosteroid kullanımı (p=0,004) açısından anlamlı farklılıklar vardı. Lökosit sayısı (p=0,003), üre (p=0,029), D-dimer (p=0,021), kreatin kinaz-MB (p=0,003) ve troponin (p<0,001) değerlerinde istatistiksel anlamlı farklılıklar tespit edildi. Ancak yoğun bakım ünitesine yatış (p=0,174) ve ölüm oranı (p=1,000) ve bu iki klinik durum birlikte değerlendirildiğinde tedavi başarısızlığı (p=0,505) iki grup arasında fark izlenmedi.

Sonuç: Çalışmamızın sonuçlarına göre kolşisin tedavisinin COVID-19 hastalarının prognozu üzerine etkisi yoktur. COVID-19 enfeksiyonu tedavisinde kolşisin tedavisinin tedavisinin rolünü araştıran prospektif çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: COVID-19 virüs enfeksiyonu, kolşisin, mortalite oranı, yoğun bakım.

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Introduction

Coronavirus Disease 19 (COVID-19) continues to spread rapidly worldwide. The pandemic process has directed clinicians to use traditional and new drugs for managing the disease. For the treatment and prophylaxis of the disease, many are being tested worldwide. Although treatment protocols have been developed in most countries to reduce the disease's mortality, no drugs or natural compounds have been found for prevention and treatment. Treatment strategies focusing on reducing the immune system's excessive activation have come to the fore in the search for effective COVID-19 management [1].

It is aimed to prevent complications that develop during the natural course of COVID-19 disease, including acute respiratory distress syndrome, cardiovascular involvement, renal damage, multi-organ failure with anti-inflammatory treatments [2, 3]. In this context, it has been suggested that colchicine may be an alternative option in the treatment of COVID-19 together with other drugs with anti-inflammatory properties [4, 5].

Colchicine is an ancient drug that has long been used to treat familial Mediterranean fever, Behcet's Disease, gout, pericarditis, and some viral infections [4, 6]. In the treatment of COVID-19, colchicine may act through different inflammatory pathways, such as inhibition of neutrophil adhesion, chemotaxis, and migration, inhibition of inflammasome, reduction of the production of superoxide ions, reduction of the production of inflammatory cytokines [4]. In randomized controlled experimental studies, the benefit of colchicine treatment in the treatment of COVID-19 has been demonstrated [7-9].

The study aimed to retrospectively investigate the effectiveness of colchicine treatment in patients hospitalized and followed up due to COVID-19 infection.

Material and methods

Study

The study was retrospectively planned between October 2020 and October 2021 at the Clinic of Infectious Diseases and Clinical Microbiology, Fatsa State Hospital in Ordu, Turkey. The local ethical committee approved the study (Ordu University, Clinical Research Ethics Committee, 2021/230). The study was conducted in compliance with Good Clinical Practice requirements and the Declaration of Helsinki. An informed consent form from patients could not be obtained since it was a retrospective study and no health care intervention was planned on patients.

Patients

Patients aged >18 years and <95 years, hospitalized in the COVID-19 clinical wards and diagnosed with COVID-19 by SARS COV2 Polymerase Chain Reaction studied from nasopharyngeal swab samples were included. Patients who were hospitalized less than three days due to COVID-19, aged >95 years and <18 years, treated in the intensive care unit (ICU), and transferred to the clinical wards from the ICU were excluded from the study. One hundred ten patients received colchicine (0.5 mg twice per day) + other treatment modalities according to the COVID-19 Guideline of Turkey Ministry of Health (favipiravir + corticosteroid + anticoagulant + symptomatic treatment) were added to the study group. With a 1:2 ratio, 220 patients treated with other than colchicine were randomly selected for the control group. Demographic data, colchicine use, duration and dosage of colchicine treatment, comorbid conditions, antibiotic and corticosteroid use, COVID-19 vaccine status, laboratory parameters, length of hospital stay, admission to the ICU, and mortality characteristics of all patients were recorded. Clinical improvement in the patients' follow-up was considered treatment success, and admission to the intensive care unit or mortality was considered a treatment failure. The patient's medical records were obtained by scanning our hospital's automation system.

Statistical Analysis

The data in the study were obtained retrospectively from the hospital automation system and uploaded to the IBM SPSS v.26 package program. Mean (± standard deviation) and min-max values were given for quantitative variables, and number (percentage) values were given for qualitative variables. Chi-square test for categorical variables and Man-Whitney U test for non-normally distributed independent quantitative data were analyzed. $P < 0.05$ was accepted as a statistical significance level.

Results

The study included 110 patients in the study group and 220 patients in the control group. The demographic characteristics of the patients, duration of hospitalization, antibiotic and corticosteroid treatment, COVID-19 vaccine status, presence of comorbid disease, ICU admission, and mortality outcomes are in Table 1. The mean duration of the colchicine treatment was 7.88±4.02 days, with a range from 3 to 29 days.

There were significant differences between age, antibiotic use, and corticosteroid dosage of the two arms. The mean age was significantly higher in the control group than the study group (p=0.001). Antibiotic use and high dosage corticosteroid treatment were significantly higher in the study group (p= 0.002 and p=0.004).

The most common coexisting disease was hypertension (63%), followed by chronic obstructive pulmonary disease and asthma (27.3%) for all patients. There was no significant difference in the proportion of comorbidities between the two groups (p=0.855).

The mean values of white blood cell count (p=0.003), urea (p=0.029), D-dimer (p=0.021), creatine kinase-myocardial band (p=0.003), and troponin (p=0.000) were statistically significantly higher in the control group than those in the study group (p<0.005) (Table 2). The mean value of neutrophil count was higher in the study group (p=0.001). In terms of other parameters, no significant difference was observed between the two groups (Table 2).

It was observed that a total of ten patients were transferred to the ICU, one (0.9%) in the study group and nine (4.1%) in the control group during the follow-up. There were four patients with mortality; three (1.4%) in the control group and one (0.9%) in the study group. The rates of treatment failure (ICU admission +mortality) were 5.45% and 1.8% in the control and study groups. Although there were more patients with treatment failure in the control group, the difference in the treatment failure rate between the groups was insignificant (p=0.505) (Table 1).

Discussion

According to our results, colchicine treatment with a dosage of 0.5 mg twice daily did not affect the treatment of COVID-19 patients. Although there were more patients with ICU admission and mortality in patients without colchicine treatment, there was no statistically significant difference between the two groups in terms of treatment failure.

Table 1. Baseline demographic and clinical characteristics of the groups.

		Control group (n=220)	Study group (n=110)	p
Age (year) †		64.95±15.92	59.37±14.78	0.001
Gender ‡	Male	106 (48.2)	59 (53.6)	0.350
	Female	114 (51.8)	51 (46.4)	
COVID-19 vaccine status ‡	Unvaccinated	22 (10)	2 (1.8)	0.781
	1 dose	7 (3.1)	8 (7.2)	
	2 doses	95 (43.2)	45 (41)	
	3 doses	25 (11.3)	13 (11.8)	
	4 doses	2 (1)	0 (0)	
	No information	69 (31.4)	42 (38.2)	
Comorbidity ‡		172 (78.9)	87 (79.1)	0.855
Antibiotic use ‡		175 (79.5)	102 (92.7)	0.002
Corticosteroid dosage ‡	<250 mg	192 (87.3)	82 (74.5)	0.004
	≥ 250 mg	28 (12.7)	28 (25.5)	
Intensive care unit admission ‡		9 (4.1)	1 (0.9)	0.174
Mortality ‡		3 (1.4)	1 (0.9)	1.000
Treatment failure ‡		12 (5.45)	2(1.8)	0.505
Length of hospital stay †		7.73±3.77	8.48±5.26	0.354

†: mean standard deviation, ‡: n (%)

Table 2. Laboratory parameters of the groups.

Laboratory parameters †	Control group (n=220)	Study group (n=110)	p
White blood cell count (10^3/µL)	8.20±3.84	7.1±3.70	0.003
Hemoglobin (g/dL)	12.63±1.88	12.97±1.66	0.152
Platelet count (10^3/µL)	213.08±85.71	200.35±75.80	0.212
Neutrophil count (10^3/µL)	6.43±3.65	6.07±7.87	0.001
Lymphocyte count (10^3/µL)	1.19±0.64	1.20±0.59	0.724
Urea (mg/dL)	43.51±24.95	37.06±20.06	0.029
Creatinine (mg/dL)	1.05±0.76	1.03±0.87	0.877
Alanine aminotransferase (U/L)	28.3±29.65	28.74±32.58	0.827
Aspartate aminotransferase (U/L)	28.3±29.65	35.63+39.51	0.240
Gamma-glutamyltransferase (U/L)	55.36±114.85	45.85±57.98	0.836
Alkaline phosphatase (U/L)	93.60±73.31	74.3±38.71	0.093
C-Reactive Protein (mg/dl)	98.66±72.91	85.41±66.02	0.136
D-dimer (ng/ml)	898.1±1195.37	614.33±849.88	0.021
Ferritin (µg/L)	483.39±592.46	342.32±286.43	0.081
Creatine kinase-MB (ng/ml)	1.94±2.17	1.27±1.12	0.003
Troponin (ng/ml)	0.14±0.31	0.08+0.13	<0.001

†: mean ± standard deviation

While there are studies suggesting that colchicine is beneficial in treating COVID-19 infection by suppressing the cytokine storm, there are also studies reported to the contrary [10-13]. In a prospective open-label randomized planned GRECCO-19 study, 105 patients who were followed up in the hospital were evaluated. Clinical deterioration was observed at a lower rate in the group receiving colchicine [7]. In another multicenter, randomized, double-blind study in which 4488 patients were evaluated, hospitalization and mortality were lower in the group receiving colchicine treatment among COVID-19 patients who were followed up without hospitalization for one month [14]. Other studies show that colchicine treatment reduces mortality in patients with COVID-19 [15,16]. However, some meta-analyses and reviews about colchicine treatment for COVID-19 do not suggest a definite benefit due to the low number of randomized controlled trials [13,15]. Our study did not find a significant impact of colchicine on treatment failure. Prospective studies with a larger sample size are needed to clarify the controversy about the prognostic effect of colchicine on COVID-19 infection.

Comorbid diseases, corticosteroid use, vaccination status, hypercoagulation, and increased risk of thrombosis are other important parameters affecting the patient prognosis in cases of COVID-19 [17-19]. In addition, the incidence of primary or secondary bacterial infections in COVID-19 cases has been reported as 0-6% to 3-8% [20,21]. For this reason, the use of appropriate antibiotics is another factor that may affect the prognosis [20]. In our study, no significant difference was observed between the two groups regarding comorbid diseases and vaccination status. Considering the higher use of high-dose corticosteroids in the case group, it can be assumed that clinicians may have used colchicine treatment for patients with a more severe course. However, some of the laboratory parameters associated with a severe course on admissions, such as D-dimer, CK-MB, and troponin, were significantly higher in the control group. Such differences might be regarded as the confounder factors while evaluating the effectiveness of colchicine.

Another factor why the results of our study differ from other studies may be the lower treatment dose and shorter treatment period. In the GRECCO-19 study, the colchicine dose was planned as 1.5 mg for the first dose and 2x0.5 mg for the maintenance treatment after one hour for three weeks [7]. In the COL-COVID study, the first dose was planned at 1.5 mg in the 48 hours, and the maintenance treatment was planned as 2x0.5 mg for 28 days [9]. In the RECOVERY study, the first dose was 1 mg, and the maintenance dose was 2x0.5 mg for ten days or until discharge [22]. Unlike these studies, no loading dose was applied to the patients in our study. It was observed that treatment was given at a dose of 2x0.5 mg starting from hospitalization. Based on the current findings, standardization has not yet been established for the dose of colchicine in the treatment of COVID-19.

The major strength of our study was that it is the first comparative case-control study in our country investigating the efficiency of colchicine in COVID-19 infection.

Limitations of this study include a small sample size. The significant differences between the two arms in terms of corticosteroid use and laboratory parameters on admission might be the confounding factors that impacted the outcomes.

In conclusion, although colchicine has been one of the preferred anti-inflammatory treatments in the treatment of COVID-19, we did not prove its efficiency in the prognosis of COVID-19 infection. Our findings showed no difference in duration of hospitalization, admission to ICU, or mortality. Studies continue with large sample sizes for colchicine treatment efficacy and dose standardization to reach a clear global treatment dose standardization. New randomized controlled trials will be beneficial to conclude a definite suggestion.

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