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Coronavirus Pandemic

Reducing length of hospital stay with colchicine

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Abstract

Introduction: Colchicine is an ancient agent with well-known anti-inflammatory effects and commonly used in treatment of hyperinflammatory conditions. It has been argued that colchicine could be an appropriate treatment option in COVID-19 to control hyperinflammatory response. Here in this study, we aimed to investigate the impact of colchicine on outcomes of COVID-19 in our inpatient cohort.

Methodology: In this retrospective cohort study, hospitalized COVID-19 patients were investigated. Demographics, comorbidities, COVID-19 symptoms, laboratory findings on admission and discharge, baseline and seventh day oxygenation status, rates of mortality, intensive care unit admission, administration of other anti-inflammatory treatments and length of hospital stay were compared between patients who received standard of care medications and who received colchicine additionally.

Results: Three hundred and thirty-six patients were included in the study (171 standard of care, 165 standard of care plus colchicine). The median length of hospital stay in colchicine group was significantly shorter. Rates of admission to intensive care unit, anti-inflammatory treatment administration and mortality did not differentiate between standard of care and colchicine groups. However, reduced rates of mortality and ICU admission were observed in patients who received colchicine with a dose of 1 mg/day when compared to patients who received 0.5 mg/day.

Conclusions: Our study demonstrated that COVID-19 patients who received colchicine in addition to standard of care had shorter hospital stay. Our results further support the use of colchicine in treatment of COVID-19, particularly with a dose of 1 mg/day.

Key words: COVID-19; colchicine; outcome; mortality; hospitalization.

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Introduction

Factors related with disease severity in coronavirus disease 2019 (COVID-19) have not been fully understood. Regardless, increased inflammatory response and hypercoagulation are considered to be two of the major aspects in severe COVID-19 [1]. Hyperinflammation in COVID-19 manifests as an exaggerated and dysfunctional innate immune reaction resembling other autoinflammatory conditions such as macrophage activation syndrom [2]. Clinical manifestations of this hyperimmune response comprise fever exceeding 38.4 °C, leukocytosis, macrocytosis, lymphopenia, anemia or thrombocytopenia. Additional findings are extremely high acute phase reactants, hyperferritinemia (exceeding three times the upper limit), increased fibrinogen and transaminase levels [3].

Colchicine, an alkaloid derived from *Colchicum autumnale,* inhibits intracellular microtubules leading to alterations in various inflammatory processes including superoxide production, neutrophil chemotaxis and adhesion by affecting the cytokine network through interleukin (IL) 1β inhibition [4,5]. As a potent anti-inflammatory agent, colchicine has been used in many inflammasome-mediated auto-inflammatory conditions such as familial Mediterranean fever (FMF), Behçet's disease, crystal induced arthritis and recurrent pericarditis [6].

Colchicine has also been demonstrated to have antithrombotic effects. It has been revealed that colchicine has potential to prevent thrombus formation via inhibiting neutrophils and α-defensin secretion [7]. Furthermore, due to its impact on the microtubules, colchicine transforms normal discoid platelets into irregular structures and suppress thrombocyte activation by reducing the calcium influx into the cells [8].

Colchicine has previously been used in treatment of viral-mediated inflammatory conditions such as myocarditis and pericarditis [7,9]. It has been argued that colchicine could be an appropriate treatment option in COVID-19 to control hyperinflammatory response considering the increased inflammasome activity in COVID-19 [10]. Currently, there is no definitive treatment for COVID-19 infection and colchicine has been studied with various other anti-inflammatory agents [11].

Here in this study, we aimed to investigate the impact of colchicine on outcomes of COVID-19 in our inpatient cohort. We also analyzed whether dose and initiation time of colchicine treatment further affects the disease course.

Methodology

In this retrospective cohort study, 402 patients over 18 years of age, who were admitted to the Ankara City Hospital, Internal Medicine inpatient clinic between August 30 and December 31, 2020 due to COVID-19 were evaluated for eligibility. Diagnosis of COVID-19 was confirmed with a recorded positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test from nasopharyngeal swab. Patients with oxygen need and persistent fever and/or elevated C-reactive protein (CRP) levels despite standard of care treatment were enrolled. Patients who were under 18 years of age, patients with pregnancy, psychiatric disease and malignancy were excluded. Demographics, comorbidities, COVID-19 symptoms, treatments administered for COVID-19, laboratory findings on admission and discharge, baseline and seventh day oxygenation status were recorded. Mortality, intensive care unit (ICU) admission, length of hospital stay and administration of anti-inflammatory treatment in addition to colchicine (systemic glucocorticoids, anakinra, tocilizumab, intravenous immunoglobulins) were set as outcome measures. The data was compared between patients who received standard of care (SOC) medications (favipiravir, hydroxychloroquine, low molecular weight heparin, acetylsalicylic acid or dipyridamole) and who received colchicine in addition to SOC. Colchicine recipients were subgrouped thereafter according to onset of colchicine administration (within 48 hours of admission and after 48 hours of admission) and colchicine dose (0,5 mg/day and 1 mg/day) and further comparisons were made.

Hospitalization, treatment, management and discharge decisions were made in accordance with the guidelines set by Turkish Health Ministry [12]. Permission from Ministry of Health was taken for conduction of this study. Ethical approval was waived due to the retrospective nature.

Statistical analysis was made by Statistical Package for Social Sciences version 22. Normality of variables was analyzed by Shapiro-Wilk test. Continuous variables were expressed either as mean ± standard deviation or as median and minimum-maximum values according to normality. While student's t-test was used for the variance of data with normal distribution, variance of data that were not normally-distributed was examined by Mann Whitney U test. x^2 test was used for comparison of categorical variables and they were presented by numbers and percentages. p values < 0.05 were considered statistically significant.

Results

Three hundred and thirty-six patients were included in the study (171 SOC, 165 SOC plus colchicine). The patient demographics, comorbidities and symptoms were presented in Table 1. No significant differences were observed between groups except for presence of fever which was more frequent in colchicine recipients (31. 6 % *vs*. 44.8 %, $p = 0.012$). Cough and dyspnea were the most common symptoms in both groups.

Laboratory tests were presented in Table 2. Discharge CRP levels were significantly lower in colchicine plus SOC group (median (IQR), 10 (24.4) mg/dL *vs*. 7 (20) mg/dL, $p = 0.03$), while discharge creatinine kinase and transaminase levels were higher. Baseline need for oxygen support was 64.9% in the SOC group while it was 53.9% in the SOC plus colchicine group. The number of patients requiring oxygen treatment was reduced to 45% and 30.9% respectively on the seventh day of treatment without significant difference (Table 3).

The median length of hospital stay in colchicine plus SOC group was significantly shorter when compared to the SOC group (median (IQR), 9 (5) *vs*. 12 (10) days, $p < 0.001$) (Table 4). No significant difference was observed between patients who received colchicine within 48 hours of admission and after 48 hours of admission (Table 5).

Rates of admission to ICU, anti-inflammatory treatment administration and mortality did not differentiate between SOC and SOC plus colchicine groups (Table 4). However, reduced rates of mortality and ICU admission were observed in patients who received colchicine with a dose of 1 mg/day when compared to patients who received 0.5 mg/day (Table 6).

Table 1. Demographics, comorbidities and COVID-19 symptoms in patients who received standard of care medical treatment *vs*. standard of care medical treatment plus colchicine.

	Standard of care (n = 171)	Standard of care plus colchicine (n = 165)	*p*
Male sex, n (%)	93 (54.4)	99 (60)	0.299
Mean age, years, mean ± SD	63.91 (15.13)	62.72 (14.37)	0.46
COVID-19 symptoms, n (%)			
Cough	83 (48.5)	85 (51.5)	0.585
Fever	54 (31.6)	74 (44.8)	0.012
Dyspnea	83 (48.5)	95 (57.6)	0.097
Headache	15 (8.8)	9 (5.5)	0.238
Back pain	9 (5.3)	8 (4.8)	0.862
Arthralgia	9 (5.3)	7 (4.2)	0.66
Myalgia	79 (46.2)	64 (38.8)	0.170
Nausea and vomiting	40 (23.4)	21 (12.7)	0.011
Anosmia	3 (1.8)	5 (3)	0.44
Ageusia	16 (9.4)	14 (8.5)	0.77
Comorbidities, n (%)			
Hypertension	98 (57.3)	79 (47.9)	0.083
Diabetes	54 (31.6)	38 (23)	0.079
Asthma	11 (6.4)	15 (9.1)	0.362
COPD	15 (8.8)	7 (4.2)	0.093
CHD	54 (31.6)	51 (30.9)	0.895
Renal disease	33 (19.3)	20 (12.1)	0.07

COVID-19: coronavirus disease 2019; COPD: chronic obstructive pulmonary disease; CHD: chronic heart disease.

Table 2. Baseline and discharge laboratory parameters in standard of care *vs*. standard care plus colchicine groups.

	Baseline			Discharge		
	Standard of care (n = 171)	Standard of care plus colchicine (n = 165)	*p*	Standard of care (n = 171)	Standard of care plus colchicine (n = 165)	*p*
Creatinin, [mg/dL]	1.01 (0.74)	0.93 (0.41)	0.058	0.93 (0.62)	0.88 (0.42)	0.243
AST, [U/L]	33 (28)	38 (26.5)	0.093	29 (24)	37 (32)	< 0.0001
ALT, [U/L]	24.5 (27.5)	31 (26)	0.034	38 (43)	61 (57)	< 0.0001
LDH, [U/L]	305 (189)	319 (165)	0.323	290 (154)	290 (150.75)	0.858
CRP, [mg/L]	59.5 (105.25)	48 (91)	0.655	10 (24.4)	7 (20)	0.03
ESR, [mm/h]	41.5 (29)	39.5 (29.75)	0.812	27 (37.75)	24 (43)	0.588
Ferritin, [µg/L]	277.5 (589)	388 (540)	0.271	312 (597)	337 (526)	0.588
WBC, [10^9 / L]	5.73 (3.53)	5.81 (3.56)	0.704	7.76 (5.13)	7.37 (4.58)	0.767
Lymphocyte, (10^9 /L)	0.95 (0.67)	0.90 (0.67)	0.784	1.27 (1.01)	1.34 (1.01)	0.099
Albumin	39.6 (5.57)	39.4 (5.98)	0.422	35 (8.09)	36.07 (6.48)	0.015
CK	101 (123)	97 (173)	0.565	34 (35)	44 (48.5)	0.017
D-dimer	0.83 (1.32)	0.76 (0.75)	0.225	0.64 (1.34)	0.62 (0.76)	0.419
Fibrinogen,[g/L]	4.61 (1.88)	4.68 (1.95)	0.642	3.61 (1.68)	3.78 (1.87)	0.092

All values are presented in median(IQR); AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; CRP: c-reactive protein; ESR: erithrocyte sedimentation rate; WBC: white blood count; CK: creatinine kinase.

Table 3. Oxygenation status at baseline and seventh day of treatment in groups.

	Baseline			7th day of treatment		
	Standard of care (n = 171)	Standard of care plus colchicine (n = 165)	*p*	Standard of care (n = 171)	Standard of care plus colchicine (n = 165)	*p*
Without oxygen supplement	60 (35.1)	76 (46.1)	0.13	94 (55)	114 (69.1)	0.19
Nasal cannula or facemask	109 (63.7)	86 (52.1)		61 (35.7)	39 (23.6)	
High flow nasal cannula	2 (1.2)	2 (1.2)		5 (2.9)	4 (2.4)	
Non-invasive mechanical ventilation	0 (0)	1 (0.6)		2 (1.2)	1 (0.6)	
Invasive mechanical ventilation	0 (0)	0 (0)		8 (4.7)	6 (3.6)	
Exitus	0 (0)	0 (0)		1 (0.6)	1 (0.6)	

All values are presented in number (%).

Discussion

Our results demonstrated that length of hospital stay was significantly shorter in colchicine recipients. Furthermore, mortality and ICU admission rates were significantly lower in patients who received colchicine with a dose of 1 mg/day when compared to patients who received 0.5 mg/day.

SARS-CoV 2 usually causes a mild disease but it can progress to a fatal illness with acute respiratory failure, shock and severe damage in vital organs [13]. SARS-CoV-2 is considered to activate nod-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome leading to cellular death [14]. Colchicine has the capability of suppressing NLRP3 inflammasome production by altering microtubule formation and deteriorating mitochondrial positioning of inflammasome proteins [15,16]. Disruption of inflammasome activation by colchicine reduces IL 1β, IL 6, tumor necrosis factor (TNF) production, chemotaxis of neutrophils and macrophages [1]. The GRECCO-19 trial established the beneficial effects of colchicine in management of COVID-19 [17].

Neutrophil extracellular trap (NET) production or NETosis, carried out by activated neutrophils, is a way of cell death similar to apoptosis and necrosis. NETosis causes cellular damage either directly or through autoimmune mechanisms [18]. Increased cytokines in SARS-CoV-2 cause lung damage in a way resembling acute respiratory distress syndrome (ARDS) and interstitial pneumonia induced by NETosis [19]. In a study that evaluates the effects of colchicine treatment on lung damage and NETosis, it has been debated that with decreased neutrophil activation and chemotaxis to the lung, colchicine reduced acute lung injury (ALI), respiratory distress and lung NETosis [20].

Table 4. Outcomes in patient groups.

	Standard of care (n = 171)	Standard of care plus colchicine (n = 165)	*p*
Length of hospital stay, days, median (IQR)	12 (10)	9 (5)	< 0.0001
Rate of anti-inflammatory treatment inititation, n(%)	117 (68.4)	115 (69.7)	0.80
Rate of intensive care unit admission, n(%)	37 (21.6)	30 (18.2)	0.42
Mortality, n(%)	19 (11.1)	16 (9.7)	0.67

IQR: interquartile range

Table 5. Pairwise comparisons of outcomes in recipients of colchicine within 48 hours of admission, after 48 hours of admission and standard of care.

	Standard of care (n = 171)	Standard of care plus colchicine within 48 hours (n = 129)	Standard of care plus colchicine after 48 hours (n = 36)	*p**	*p*¶	*p*¥
Length of hospital stay, days, median (IQR)	12 (10)	9 (6)	8 (3.75)	< 0.001	0.002	0.301
Rate of anti-inflammatory treatment inititation, n (%)	117 (68.4)	89 (69)	26 (72.2)	0.91	0.65	0.709
Rate of intensive care unit admission, n (%)	37 (21.6)	22 (17.1)	8 (22.2)	0.32	0.93	0.47
Mortality, n (%)	19 (11.1)	12 (9.3)	4 (11.1)	0.61	1	0.74

IQR: interquartile range; *: standart of care *vs*. standard of care plus colchicine within 48 hours; ¶: standard of care *vs*. standard of care plus colchicine after 48 hours; ¥: standard of care plus colchicine within 48 hours *vs*. after 48 hours.

Table 6. Pairwise comparisons of outcomes in recipients of colchicine 0.5 mg/day, 1 mg/day and standard of care.

	Standard of care (n = 171)	Standard of care plus colchicine 0.5 mg/day (n = 37)	Standard of care plus colchicine 1 mg/day (n = 128)	*p**	*p*¶	*p*¥
Length of hospital stay, days, median (IQR)	12 (10)	9 (8)	9 (6)	0.107	< 0.0001	0.33
Rate of anti-inflammatory treatment inititation, n(%)	117 (68.4)	26 (70.3)	89 (69.5)	0.826	0.9	0.931
Rate of intensive care unit admission, n(%)	37 (21.6)	12 (32.4)	18 (14.1)	0.161	0.09	0.011
Mortality, n(%)	19 (11.1)	7 (18.9)	9 (7)	0.193	0.231	0.031

IQR: interquartile range; *: standart of care *vs*. standard of care plus colchicine 0.5 mg/day; ¶: standard of care *vs*. standard of care plus colchicine 1 mg/day; ¥: standard of care plus colchicine 0.5 mg/day *vs*. 1 mg/day.

ARDS and/or ALI is frequent in COVID-19 patients. NLRP3 has been displayed to be an important pathophysiological component in development of ARDS and ALI [21]. In COLCORONA study, in which approximately 4,500 COVID-19 patients were evaluated, it has been demonstrated that colchicine reduced hospital admissions by 25%, need for mechanical ventilation by 50% and mortality by 44% [22]. In the study conducted by Scarsi *et al*., colchicine was compared with standard COVID-19 treatment (hydroxychloroquine and/or intravenous dexamethasone; and/or lopinavir/ritonavir) and a better survival rate was reported in patients treated with colchicine (21-day survival; colchicine plus SOC 84.2% *vs*. SOC 63.6%; $p = 0.001$) [23]. Another study carried out by Lopez *et al*. demonstrated that discharge from the hospital on the tenth day was detected to be higher for patients who took colchicine, furthermore a greater reduction was observed in CRP levels in colchicine recipients [24]. In our study, we detected no difference with colchicine in terms of mortality, ICU admission and need for anti-inflammatory treatment. However, rates of ICU admission and mortality were significantly lower in patients who received colchicine 1 mg/day in comparison to those who received 0.5 mg/day. Additionally, we detected that there was a significant difference in discharge CRP values between SOC and SOC plus colchicine groups.

In an animal study, it has been revealed that colchicine reduced lung damage by 61% and improved oxygenation considerably by increasing lung PaO_2/FiO_2 [20]. In our study, although the need for oxygen in SOC group and in SOC plus colchicine group were similar, rate of ICU admission was found to be significantly lower in the group that received colchicine with a dose of 1 mg/day in comparison to the group that received 0.5 mg/day.

Our study possesses the typical limitations of a single-center retrospective case study. Randomized-controlled studies are needed to better demonstrate the effects of colchicine.

To date, there are no curative pharmacological therapies for COVID-19-induced respiratory failure. The need for hospitalization and ICU admission has become a global problem during the pandemic. Thus, shortening the length of hospital stay even with a relatively cheap agent such as colchicine may be important in management of COVID-19. Gastrointestinal side effects can be observed in about 10% of the patients with colchicine and do not usually necessitate cessation of treatment [25]. All in all, our results further support the use of colchicine in treatment of COVID-19, particularly with a dose of 1 mg/day. Larger and prospectively designed trials would further determine the efficacy of colchicine in COVID-19 with optimum dose and timing for administration.

Authors' contributions

OK, AE, SCG, AO, OK and IA designed the study. OK, AE, OK, ESS, OI and AO examined cases. OK, BA, OK, ACK, IA and SCG collected data. AE, OK, BA, ACK, OI and İA searched the literature. OK, AE, OK, SCG and IA interpreted and discussed the results. ESS, OI, EG, ACK, OK, AO and IA analyzed data. OK, AE, SCG, BA and EG wrote the paper. EG, AE, OK, AO, OK and SCG revised the manuscript critically for important intellectual content. AE, OK, AO, OK, BA, IA, ESS, ACK, EG, SCG and OI contributed to the final version of the manuscript. All authors have reviewed and approved the final version of the article, including the authorship list.

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