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Evaluation of Pentoxifylline and Colchicine Administration on Clinical Outcomes of Hospitalized Patients with COVID-19

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ABSTRACT

Background and Objective: The COVID-19 pandemic has caused numerous cases of respiratory failure and death. Due to the little information available about the disease treatment, we decided to evaluate the effectiveness of pentoxifylline and colchicine in preventing the progression of the disease to the stage of deterioration in hospitalized patients with COVID-19.

Methods: In this double-blind randomized clinical trial, 120 patients (60 in the control group and 60 in the intervention group) with COVID-19 over 40 years of age with moderate and severe disease were examined in Shafa Khorramabad Hospital. The intervention group received pentoxifylline at a dose of 400 mg every 12 hours and colchicine at a dose of 0.5 mg daily in addition to standard treatment, and the control group received the standard treatment regimen alone. In both groups, clinical and laboratory criteria in blood were compared. Also, the duration of hospitalization, the duration of the intensive care unit admission, the rate of recovery (reduction of disease symptoms and increase of blood oxygen), and death were compared.

Findings: There was no significant difference between the age, weight, gender, medical history and early symptoms of the two groups. The two groups differed significantly in the number of people hospitalized in the ICU (17 patients, 28.3% in the control group) and (6 patients, 10% in the intervention group) and the number of people with persistent fever (24 patients, 30% in the control group), and (12 patients, 20% in the intervention group) ($p<0.05$). However, there was no significant difference between the two groups in terms of mortality, clinical and laboratory results.

Conclusion: Based on the results of this study, prescribing the two drugs, pentoxifylline and colchicine, may prevent the critical stage of the disease.

Keywords: *COVID-19, Colchicine, Pentoxifylline.*

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Introduction

COVID-19 is a new coronavirus that has caused a worldwide pandemic of respiratory infections since December 2019. A single-stranded RNA virus induces COVID-19 infection (1, 2). It causes indirect damage to the heart, lungs, and organs through innate, humoral, and cellular immune reactions (3). A "cytokine storm" is an excessive inflammatory response in COVID-19 patients, leading to acute respiratory distress syndrome (ARDS). This is a frequent cause of death. (4). Pro-inflammatory cytokines such as interleukin 1 (IL-1) and tumor necrosis factor (TNF-α) play an essential role in virus-induced inflammation (5). COVID-19 induces hyper activation of the NLR family pyrin domain 3 (NLRP3) inflammasome, resulting in the release of cytokines and chemicals (6). Patients with severe COVID-19 have higher serum levels of pro-inflammatory cytokines, chemokines, C-reactive protein (CRP), and lymphopenia and neutrophilia than people with mild disease or healthy individuals (7). Neutrophils produce neutrophil extracellular traps (NETs), which damage lung epithelial cells (8).

Finding appropriate therapeutic options is essential to managing the pandemic and reducing mortality, but only corticosteroids have been shown to improve prognosis, so more appropriate drugs are needed (9). Two of the most useful anti-inflammatory drugs are colchicine and Pentoxifylline (PTX). Colchicine was first approved by the US Food and Drug Administration in October 2009 (10). Colchicine aggregates in monocytes and neutrophils, affects chemotaxis of inflammatory cells, and suppresses the expression of E-selectin, which is responsible for binding leukocytes to endothelial cells (11). Colchicine is used to treat auto-immune disorders such as gout, pericarditis, and cardiomyopathy syndrome (12). PTX is another anti-inflammatory drug. PTX is a phosphodiesterase (PDE) inhibitor that increases cyclic adenosine monophosphate (cAMP) levels while inhibiting protein kinase (PKA), thereby reducing the production of proinflammatory cytokines (13). In vitro, PTX alters the renin-angiotensin (RAS) system by decreasing the expression of angiotensin 1 receptor (AT1R) (13). PTX is used in neonatal septic shock treatment due to its effects on glutathione regeneration, mitochondrial viability, TNF- production, and microvascular blood flow preservation (14). Finding an appropriate drug response is essential for the development of new anti-inflammatory drugs against COVID-19.

This study is the first to assess the efficacy of colchicine and PTX in COVID-19 patients, potentially providing convenient and cost-effective treatment. As a result of this study, new approaches in the treatment of COVID-19 may be related to the anti-inflammatory properties of colchicine when used in combination with pentoxifylline.

Methods

After being approved by the ethics committee of Lorestan University of Medical Sciences with the code IR.LUMS.REC.1399.362 and registered in the Iranian clinical trial system with the code IRCT20200721048159N3, this clinical trial was conducted on patients admitted to Shafa Khoramabad Hospital with moderate to severe COVID-19. The Excel "RAND" function randomly places 60 patient codes in the control group and another 60 codes in the intervention group. RAND returns a uniformly distributed random real number greater than or equal to zero and less than 1.

Patients were classified according to the severity of COVID-19: patients without shortness of breath and hypoxia with upper respiratory symptoms were considered to have the mild form of the infection. Patients with a respiratory rate (RR) of more than 24/minute, breathlessness, fever, and blood oxygen saturation (SpO_2) of 90-93% without oxygen therapy on room air were categorized in the moderate form of the infection and patients with a respiratory rate of more than 30/minute, shortness of breath, fever, and

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$SpO_2 \leq 90\%$ were classified as having the most severe form of the infection. Positive RT-PCR test results and radiographic signs of COVID-19 pneumonia in the lung CT scan, as well as related clinical signs, were considered for inclusion criteria. If a patient had refractory hypoxemia, reduced awareness and hemodynamic instability, they were transferred to the intensive care unit (15). Pregnancy and lactation, history of colchicine and PTX allergy, side effects, comorbidities (such as renal failure with GFR of 30 ml/min, liver failure with bilirubin 2 mg/dL and albumin 2.8 g/dL, active gastrointestinal ulcer, neuromuscular disease, chronic diarrhea, or malabsorption), BMI of 34.9 kg/m2, active bleeding, including intracerebral hemorrhage, were all exclusion criteria. Blood samples were taken for biochemical analysis every two days. Patients were discharged from the hospital if they did not have dyspnea and had a $SpO_2 \geq 92\%$ and reduction of disease symptoms for at least 48 hours (the rate of recovery).

Following an initial evaluation of 150 patients, 20 patients were eliminated based on the exclusion criteria (twelve patients had chronic renal failure, gastrointestinal bleeding, and liver failure; five patients refused to participate in the study, and three patients were pregnant). A total of 130 patients were randomly divided into two groups. 65 patients in the intervention group received PTX and colchicine in addition to standard treatment, while 65 patients in the control group received standard treatment. Five patients in the intervention group were excluded from the research due to receiving IVIG and Octemra, while five patients in the control group were excluded with personal consent. 60 patients in each group were analyzed (Figure 1).

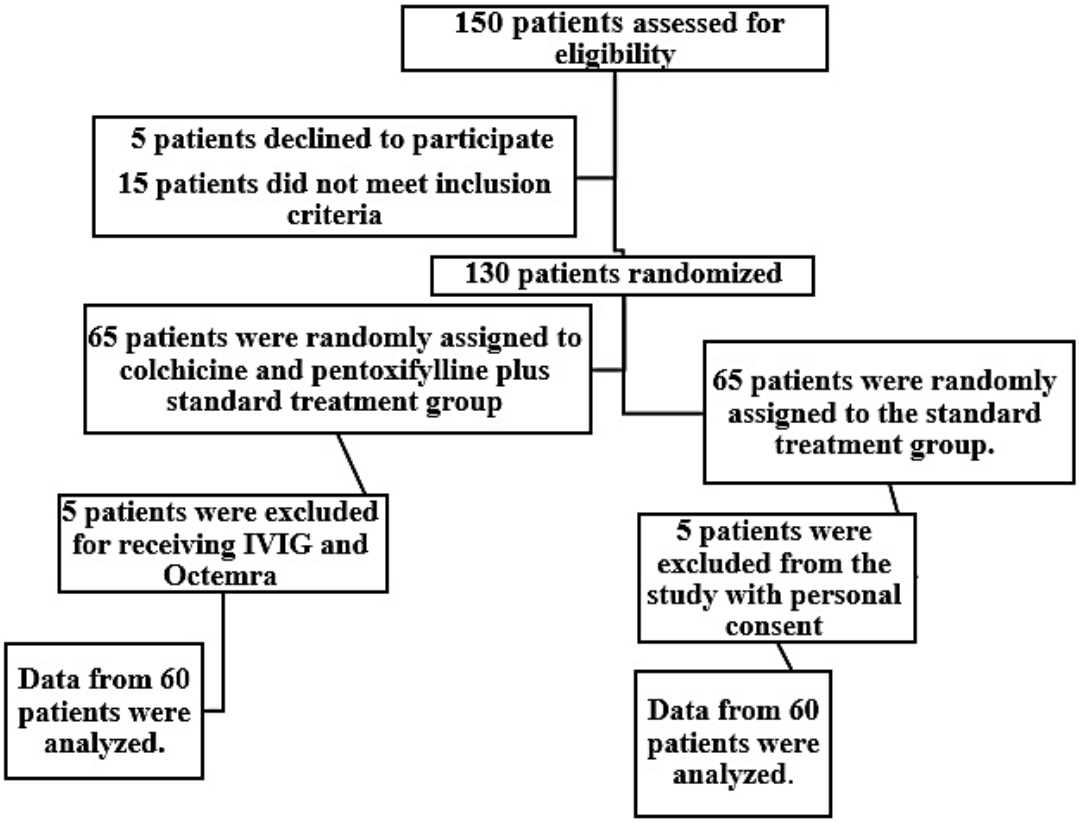

Figure 1. Study flow diagram showing selection of studies.

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The two groups matched in terms of demographic variables. Patients were given Dexamethasone (8 mg once a day) and Remdesivir (200 mg for the first day and 100 mg for the next five days) as a standard of treatment for 5-10 days, while the intervention group also received PTX (400 mg every 12 hours) and colchicine (0.5 mg once a day). The outcomes (clinical parameters) were collected, including days of hospitalization; the duration of the fever; length of time spent in the ICU; and death rate. During the study, we assessed a variety of laboratory factors, such as complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase (LDH), coagulation tests, electrolytes, urea, and creatinine tests.

SPSS statistical software (version 22.0; IBM Business, USA) was used to collect and analyze the data. The Kolmogorov-Smirnov test was performed to analyze the normality distribution. The data was described using the mean, standard deviation (SD), median, and interquartile range. The standard deviation was used to represent quantitative data with a normal distribution, whereas the median and IQR were used to explain data with a non-normal distribution. The qualitative data was characterized using frequency and percentages, and the Chi-square test was used to compare groups. To compare quantitative data, the independent t-test or Mann-Whitney, paired t-test, and repeated measures analysis of variance were utilized. $p<0.05$ was considered statistically significant.

Results

Gender, age, basic disorders, medical histories, and clinical symptoms were recorded as demographic variables. The results of comparing patients showed that age and gender were not significantly different between the two groups, the control group having a mean age of (65.63±14.21 years) with 27 females (45%) and 33 males (55%) and the intervention group having a mean age of (61.23±13.13 years) with 23 females (38.3%) and 37 males (61.7%). The mean BMI was 25.03±4.91 kg/cm^2 in the control group, but it was 26.16±5.3 kg/cm^2 in the intervention group, which was not significant. The Chi-square test showed that smoking and underlying diseases did not differ significantly between the two groups (Table 1).

Regarding the frequency of clinical symptoms in the control group, shortness of breath (51.7%), weakness or malaise (48.3%), fever (43.3%), cough (41.7%), chills (31.7%) were the most common described symptoms. Also, in the intervention group, the most frequently reported symptoms were related to shortness of breath (63.3%), cough (43.3%), fever (36.7%), weakness or malaise (35%), chill (31.7%). There was no statistically significant difference between the two groups (Table 1).

The biochemical data showed no difference between the two groups, including INR, PT, PTT, troponin C, CPK, ferritin, CRP, ESR, and D-dimer. But the amount of LDH in the intervention group (553.31±210.1) was significantly higher than the control group (499.16±171.16) ($p=0.018$) (Table 2).

Intra-group comparison showed a significant difference in the mean of temperature (T), heart rate (HR), and SpO_2 over time ($p<0.05$). Yet, no significant difference in clinical indicators over time (Table 3).

The results showed that based on intra-group comparison, there was a significant difference in red blood cells (RBC), white blood cells (WBC), platelets (PLT), hemoglobin (Hb) content, and urea over time ($p<0.05$), while the ALT index changes were significant in the control group ($p=0.014$). The WBC count was high at admission and reduced from the moderate hospitalization time to the end of treatment in control and intervention patients. These changes were statistically significant ($p<0.05$), but there was no significant difference between the two groups. RBC and hematocrit (HCT) levels in both control and intervention patients were significantly lower at admission and increased from the moderate hospitalization period to the end of treatment ($p<0.05$). PLT and urea increased significantly from admission to the end of treatment, while Hb content decreased significantly from admission to the end of treatment in both groups ($p<0.05$).

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Table 1. Demographic and Clinical information of the COVID-19 Patients

Variable	Control group (n=60) Number(%) or Mean±SD	Intervention group (n=60) Number(%) or Mean±SD	p-value
Gender			
Female	27(45)	23(38.3)	0.259
Male	33(55)	37(61.7)	
BMI (kg/m^2)	25.03±4.91	26.16±5.30	0.291
Age	65.14±63.21	61.23±13.13	0.113
Underlying diseases			
Heart disease	18(25)	20(33.3)	0.710
Diabetes	15(25)	20(33.3)	0.710
Blood pressure	29(48.3)	30(50)	0.510
Dyslipidemia	13(21.7)	20(33.3)	0.342
Asthma	6(10)	2(3.3)	0.192
Convulsions	1(1.7)	2(3.3)	0.625
Prostate hyperplasia	1(1.7)	5(3)	0.461
Gout	1(1.7)	1(1.7)	0.710
Hyperthyroidism	0(0)	2(3.3)	0.280
Iron deficiency anemia	0(0)	5(3)	0.173
Rheumatism	3(5)	0(0)	0.130
Hypothyroidism	3(5)	3(5)	0.706
Smoking			
Yes	8(13.3)	11(11.3)	0.309
No	52(86.7)	49(81.7)	
Early clinical signs			
Fever	26(43.3)	22(36.7)	0.288
Dry cough	25(41.7)	26(43.3)	0.500
Shortness of breath	31(51.7)	38(63.3)	0.134
Phlegm	1(1.7)	4(6.7)	0.182
Lethargy and weakness	29(48.3)	21(35)	0.097
Diarrhea	1(1.7)	3(5)	0.309
Headache	3(5)	2(3.3)	0.500
Shivering	19(31.7)	19(31.7)	0.578
Muscular pain	5(8.3)	8(13.3)	0.273
Loss of appetite	6(10)	8(13.3)	0.389
Vomiting and nausea	2(3.3)	4(6.7)	0.34
Dizziness	1(1.7)	3(5)	0.309

Table 2. Comparison of disease severity predictors at admission in both groups

Clinical indices and laboratory findings	Control group (n=60) Mean±SD	Intervention group (n=60) Mean±SD	p-value	Normal range
INR	1.22±0.93	0.16±0.37	0.690	1-3
PT (S)	14.32±4.5	14.94±4.8	0.431	13-16
PTT (S)	36.42±8.95	34.94±2.78	0.649	26-38
LDH (U/liter)	499.16±171.16	553.31±210.1	0.018	230-460
Troponin C (ng/liter)	5.9±10.76	8.74±20.98	0.961	<1.5
CPK (U/liter)	105.56±43.31	165.57±70.2	0.989	24-195
Ferritin (ng/ml)	691.1±491.7	673.4±403.56	0.954	39.715
ESR 1hr (mm/hr)	50.10±16.94	41.91±19.78	0.169	<20
D-dimer (ngFEU/ml)	918.07±971.7	1219.88±1434	0.438	Up to 800

INR: International Normalized Ratio, PT: Prothrombin Time, PTT: Partial Thromboplastin Time, LDH: Lactate Dehydrogenase, CPK: Creatine phosphokinase, ESR: Erythrocyte Sedimentation Rate.

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Table 3. Comparison of the mean clinical data of the studied patients with COVID-19 in intervention and control groups at the time of admission, hospitalization and discharge

Factor and group	Admission Mean±SD (interquartile range) range	Hospitalization Mean±SD (interquartile range) range	Discharge Mean±SD (interquartile range) range	Intragroup p-value	Intergroup p-value
Temperature (degrees Celsius)					
Intervention	37.2±0.47 37 (0.30)	36.85±0.16 36.9 (0.28)	36.76±0.32 36.9 (0.40)	<0.001	0.23
Control	37.2±0.54 37 (0.37)	36.0±0.96 37 (0.20)	36.93±0.23 37 (0.15)	<0.001	
Heart rate (beats per minute)					
Intervention	85.23±9.62 82 (11.25)	79.59±6.24 80 (6.85)	77.45±8.95 78 (8)	<0.001	0.541
Control	83.93±16.4 83.5 (12)	79.51±4.73 78 (6)	78.53±8.08 80 (12)	0.026	
Respirations (numbers per minute)					
Intervention	18.66±1.14 18 (1.75)	18.34±0.42 18 (1)	18.21±1.5 18 (1)	0.127	0.282
Control	18.35±1.2 18 (1)	18.41±1.1 18 (1)	18.26±0.82 18 (1)	0.654	
Systolic blood pressure (mmHg)					
Intervention	124.25±16.96 120 (20)	117.01±7.84 117 (8)	118.35±17.06 120 (18)	0.008	0.528
Control	122.46±16.9 120 (10)	115.97±8.01 115 (9)	115.01±11.5 114 (10)	0.003	
Diastolic blood pressure (mmHg)					
Intervention	78.1±9.94 80 (13.5)	72.91±5.63 73 (6)	73.35±9.16 70 (10)	0.001	0.761
Control	78.38±9.02 80 (12)	73.62±5.51 74 (9)	72.26±8.1 70 (10)	0.001	
Ambient oxygen saturation (%)					
Intervention	92.35±3.51	91.15±2.6	93.23±3.57	0.003	0.475
Control	91.55±2.82	91.12±4.12	92.45±4.73	0.038	

Regarding the Polymorphonuclear Neutrophils (PMN) percentage in the control group, there was a significant increase between the admission time and the end of the treatment time (p=0.004), but in the intervention group, there was a reduction at the admission and end of the treatment, which was not significant. Also, lymphocytes in the intervention group had a significant decline from the admission time to the end of the treatment (p=0.006). In the control group, this reduction was not significant (p=0.093).

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In general, there was no significant difference between the mean laboratory findings of mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), AST, ALP, creatinine (Cr), sodium (Na), potassium (K) at the time of onset, duration of hospitalization, and end of treatment in both groups (Table 4).

Table 4. Comparison of the mean laboratory indices of the studied patients with COVID-19 in intervention and control groups at the time of admission, hospitalization and discharge.

Index and group	Admission Mean±SD (Interquartile range) range	Hospitalization Mean±SD (Interquartile range) range	Discharge Mean±SD (Interquartile range) range	Intragroup p-value	Intergroup p-value
WBC×10^3 (cu.mm)					
Intervention	6.42±2.72 6.2 (3.60)	8.38±4.35 7.6 (4.20)	8.31±2.91 7.3 (4.45)	<0.001	0.466
Control	6.56±3.57 5.87 (3.20)	8.3±3.70 8.7 (4.52)	8.93±3.73 8.90 (4.30)	0.006	
RBC (ul)					
Intervention	4.72±0.51 4.66 (0.63)	4.37±0.4 4.38 (0.46)	4.59±0.55 4.63 (0.71)	<0.001	0.911
Control	4.57±0.55 4.51 (0.80)	4.23±0.47 4.29 (0.56)	4.33±0.55 4.37 (0.67)	0.003	
Hb (g/dl)					
Intervention	15.64±3.2 13.80 (2.15)	13.15±1.50 13.10 (1.75)	12.81±1.38 13.40 (1.68)	<0.001	0.597
Control	13.21±1.72 13.70 (2)	12.38±1.66 12.45 (1.43)	12.19±1.47 12.90 (1.50)	0.003	
HCT (%)					
Intervention	40.52±4.16 40.65 (5.57)	37.42±3.5 38.40 (4.85)	38.69±4.24 39.15 (5.25)	<0.001	0.222
Control	38.9±6.07 39.60 (5.90)	36.43±4.23 37.35 (4.55)	36.97±4.82 37.90 (4.90)	0.281	
MCV (FL)					
Intervention	86.08±5.88 86.55 (5.03)	85.68±4.93 85.50 (4.85)	84.54±6.23 84.85 (7.95)	0.128	0.580
Control	86.76±7.03 87.30 (7.45)	86.25±7.04 85.85 (7.65)	84.95±10.4 85.70 (7.30)	0.458	
MCH (Pg)					
Intervention	28.85±2.08 29.05 (2.60)	29.3±2.03 29.50 (2.27)	28.78±2.4 28.70 (2.62)	0.331	0.456
Control	28.99±2.56 28.60 (3.10)	28.83±2.46 28.75 (2.43)	28.78±2.41 28.70 (3.40)	0.516	
MCHC (g/dL)					
Intervention	33.49±1.36 33.45 (1.50)	34.16±1.10 34 (1.70)	33.98±1.31 34 (1.45)	0.233	0.428
Control	33.49±1.25 33.50 (1.70)	33.43±1.09 33.20 (1.30)	33.42±1.07 33.50 (1.20)	0.988	
ALP (U/liter)					
Intervention	182.87±62.92 167.50 (70.25)	260.07±341.63 159 (43.25)	211.61±188.31 174 (91.75)	0.511	0.494
Control	184.22±61 173 (54.50)	198.00±60.39 184 (63.50)	193.85±69.23 168.50 (118.25)	0.141	

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Index and group	Admission Mean±SD (Interquartile range) range	Hospitalization Mean±SD (Interquartile range) range	Discharge Mean±SD (Interquartile range) range	Intragroup p-value	Intergroup p-value
ALT (U/liter)					
Intervention	47.66±25.26 38 (34)	74.9±118 49 (37.50)	69.54±52.47 58 (38.75)	0.161	0.749
Control	39.85±24.18 32 (20.50)	56.09±47.8 42 (32.50)	58.4±32.06 51 (50)	0.014	
Platelet (ul)					
Intervention	173.8±54.29 106.50 (66)	204.75±69.18 198 (90.50)	213.60±77.60 207.50 (106.25)	<0.001	0.728
Control	159.7±42 150 (40)	191±61.82 180 (89)	193.71±70.19 181 (105)	0.003	
Creatinine (mg/dl)					
Intervention	1.06±0.19 1.04 (0.29)	1.00±0.16 0.98 (0.20)	1.07±0.02 1.03 (0.30)	0.079	0.197
Control	1.11±0.32 1.06 (0.35)	1.17±0.48 1.06 (0.35)	1.13±0.37 1.06 (0.34)	0.665	
Urea (mg/dl)					
Intervention	45.46±12.95 42 (14.75)	54.90±19.01 53.50 (22.75)	57.82±23.97 54.50 (22.50)	<0.001	0.060
Control	46.61±16.89 45 (18)	64.05±37.80 54 (28)	64.00±36.24 53 (28.50)	<0.001	
Sodium (meq/liter)					
Intervention	142.05±2.66 142 (3.35)	141.97±2.67 142 (4.65)	141.88±2.55 141.50 (4.40)	0.544	0.734
Control	142.89±2.98 143 (3.32)	141.81±2.37 141.7 (4.20)	141.86±2.99 141.70 (4.50)	0.589	
Potassium (meq/liter)					
Intervention	4.08±025 4.06 (0.37)	4.05±0.48 4.04 (0.46)	4.16±0.47 4.15 (0.55)	0.276	0.800
Control	4.14±0.32 4.19 (0.48)	4.18±0.62 4.37 (0.94)	4.32±0.62 4.22 (0.88)	0.324	
AST (U/liter)					
Intervention	52.89±21.50 46 (20.25)	80.18±37.70 47 (28.75)	59.88±20.00 47 (30)	0.307	0.519
Control	50.38±32.57 39 (21)	56.48±27.80 47 (26.50)	52.85±27.67 45 (33)	0.261	
PMN (%)					
Intervention	82.44±5.18 81 (7)	87.04±10.12 86 (9)	82.44±5.18 81 (7)	0.404	0.450
Control	87.44±6.02 87.70 (11.90)	84.22±5.04 84.03 (6.12)	87.44±6.02 87.70 (11.90)	0.004	
Lymphocyte (cells/l)					
Intervention	20.39±6.31 19.50 (7)	18.05±5.82 18 (7.2)	12.59±6.04 12 (10.20)	0.006	0.280
Control	18.55±6.52 18.50 (6.75)	15.43±10.4) 15 (12.3)	12.17±8.98 9.65 (16.5)	0.093	

WBC: White Blood Cell, RBC: Red blood cell, Hb: Hemoglobin, HCT: Hematocrit, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, AST: Aspartate Transaminase, ALT: Alanine Transaminase, ALP: Alkaline Phosphatase, PMN: Polymorphonuclear.

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During the study, it was found that the intervention group had a shorter duration of fever and a shorter length of hospital and ICU stays. This difference was significant ($p<0.05$) (Table 5). Also, patients who were transferred to the ICU and had a persistent fever were significantly lower in the intervention group. In the intervention group, 20 patients (33.3%) had fever and, in the control group, 24 (66.7%) patients had fever. But in terms of clinical criticality, in the intervention group, 6 patients (10%) were transferred to the ICU and in the control group, 17 patients (28.3%) were transferred to the ICU (Figure 2) ($p<0.05$). Based on vital status, two patients (3.3%) died and 58 (96.7%) were discharged from the hospital in the intervention group. In the control group, three patients (5%) died, and 57 (95%) were discharged from the hospital. This difference was not significant (Figure 2).

Table 5. Comparison of hospitalization duration, ICU admission time and fever duration of COVID-19 patients

Variable and group	Number(%)	p-value	Mean±SD (interquartile range) range	p-value
Duration of hospitalization Control Intervention	57(96.7) 58(95)	0.500	8.76±3.85 8 (3) 9.91±3.61 9 (4.75	0.026
Length of stay in ICU Control Intervention	17(28.3) 6(10)	0.01	2.97±0.95 0 (0) 4.37±2.3 0 (0)	0.018
Duration of fever Control Intervention	24(30) 12(20)	0.01	0.45±0.21 0 (0) 0.95±0.66 0 (0)	0.005

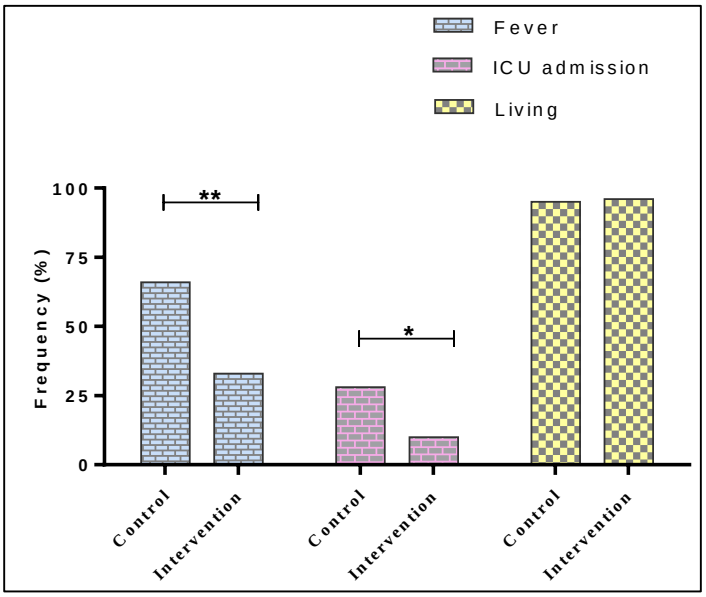

Figure 2. Effect of Co-administration of PTX and colchicine on fever, ICU admission and improvement

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Discussion

This study found that the intervention group was significantly different from the control group in terms of hospitalization time, ICU length of stay, and duration of fever. Additionally, the number of patients with fever and transferred to the ICU was lower, but there was no relationship between improvement and death in both groups. Pascual-Figal et al. recorded a 2021 study on 103 patients, divided into intervention and control groups. The intervention group received colchicine and all survived, while the control group had two deaths. Treatment with colchicine did not improve clinical status or inflammatory response in patients with COVID 19 compared to standard therapy (16). A study was conducted with 11340 (58%) eligible for the study. 5610 patients (49%) were assigned to the colchicine group, while 5730 patients (51%) were in the control group with routine care. 1173 patients in the colchicine-receiving group and 1190 in the routine care group died within 28 days, with no significant difference in patients discharged from the hospital. Colchicine was not associated with a reduction in mortality, hospitalization, or risk of mechanical ventilation or death (17). Wall et al.'s 2021 study found that PTX administration was associated with decreased CRP and a mortality rate. This study could be used to further investigate the role of these drugs in COVID-19 (18).

The study found that lymphocyte levels decreased in only the intervention group from admission to the end of treatment, while the PMN percentage increased significantly in the control group opposite of intervention group. Colchicine causes monocytes and neutrophils to congregate, modifies inflammatory cells' chemotaxis, and inhibits leukocytes adhesion to endothelial cells (11). Manenti et al. conducted a retrospective study of 141 patients with COVID-19, with 70 receiving colchicine and 71 receiving routine care. The 21-day mortality rate was 7.5% in the colchicine group and 28.5% in the control group. This study found that 21-day clinical improvement was seen in 40% of patients treated with colchicine and 26.6% of control patients. Lymphocyte levels decreased in the intervention and control groups, but were not significant (19). Maldonado et al. showed a 2021 study on 38 patients with COVID-19, with 26 randomly selected to receive PTX and standard treatment, while the rest received only standard treatment. PTX was associated a 29.61% decrease in serum LDH, but no statistically significant differences were observed in hospitalization days, mortality, or proportion of patients requiring intubation (20). Colchicine's protective effect appears to be improved by PTX.

Considering the outcomes of current study, Co-administration of two drugs, PTX and colchicine, may prevent the critical stage of the disease from entering and decrease the duration of hospitalization, thus reducing treatment costs.

Conflict of interest: The authors have no conflict of interest.

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