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Efficacy of Hydroxychloroquine versus Clarithromycin in the Improvement of Dyspnea and Cough in Patients after the Treatment of Acute-Phase COVID-19

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Abstract

Background: Post-acute COVID-19 syndrome involves the persistence of the patient's symptoms due to the residual inflammation of the acute phase.

Objectives: In the current study, we aimed to evaluate medication intervention to accelerate the improvement of prolonged respiratory symptoms in this phase.

Methods: Thirty-four patients, aged 20-50 years, in the recovery phase of COVID-19, were enrolled, who still suffered from respiratory problems even two weeks after being discharged from Rasool Akram Hospital, Tehran, Iran. They were divided into three groups based on the type of treatment for eliminating the remaining symptoms: hydroxychloroquine (HCQ, 200 mg twice daily for four weeks), clarithromycin (500 mg twice daily for four weeks), and control (receiving a placebo similar to the last two groups). At the beginning and end of the treatment, patients' dyspnea and cough were assessed using Medical Research Council and visual analog scale (VAS), respectively, their laboratory tests were checked, and they took a 6-min walk test.

Results: At the end of the treatment, the VAS of cough was 0.74 in the HCQ group, which was higher than that in the clarithromycin group. In addition, dyspnea decreased in the HCQ and clarithromycin groups by 64% and 40%, respectively, compared to the control group. Furthermore, there was a significant relationship between residual dyspnea at the end of the treatment and the severity of initial lung involvement in the acute phase.

Conclusion: Based on these findings, it can be concluded that HCQ was more effective in reducing dyspnea, compared to clarithromycin, in the recovery phase, especially in patients with milder lung involvement in the acute phase. Additionally, clarithromycin was found to be more effective in improving coughs.

Keywords: Clarithromycin, Cough, COVID-19, Hydroxychloroquine, Post-acute COVID-19

1. Background

The 2019 novel coronavirus disease (COVID-19) first emerged in Wuhan, China, in December 2019 (1). Acute respiratory distress syndrome is a major clinical manifestation in COVID-19 patients, which can cause a higher mortality rate in older adults and those with comorbidities (2).

Many patients with acute COVID-19 have involvement in their respiratory system, characterized by dry cough, dyspnea, hypoxemia, and abnormal imaging results (3).

It has been confirmed that COVID-19 infection can affect patients' long-term pulmonary, as well as physical and psychological function (4). Based on some reports, about 40%-90% of COVID-19 patients suffer from persistent symptoms following recovery from the acute phase (5, 6). Researchers use the term post-COVID-19 syndrome to describe the persistent symptoms caused by prolonged inflammation, organ damage, or non-specific effects from hospitalization or prolonged ventilation (7). According to several studies, dyspnea and fatigue are the main symptoms that persist after recovery (8-10). Histological examination of patients in the acute phase showed diffuse alveolar damage with desquamation of pneumocytes, hyaline membrane formation, as well as interstitial mononuclear inflammatory infiltrates (11), and in some cases, fibro myxoid proliferation in the intra-alveolar spaces. Pulmonary fibrosis is the termination of this prolonged inflammatory process (12). Persistent symptoms, such as cough and dyspnea, can decrease pulmonary function in patients with post-COVID-19 syndrome.

2. Objectives

This study aimed to control residual inflammation during the recovery phase using Hydroxychloroquine (HCQ) and clarithromycin, which have been confirmed to have immunomodulatory effects in controlling chronic inflammatory processes in the lungs.

3. Methods

3.1. Subjects

In this study, we recruited COVID-19 patients aged 20-50 years, who still reported symptoms such

as shortness of breath, cough, and pulmonary involvement on a CT scan two weeks after their treatment ended at Rasool Akram Hospital, Tehran, Iran. Participants were diagnosed with COVID-19 based on the World Health Organization interim guidance and confirmed by a positive real-time RT-PCR test of oropharyngeal swab specimens, during one year starting from February 2020.

All patients provided written informed consent. The selection of patients was based on a review of hospital records, follow-up phone calls after discharge, and face-to-face interviews. Those with a history of chronic cardiopulmonary diseases or long-term use of medications that might have interfered with the study results were excluded.

3.2. Study Design

We divided our COVID-19 patients into three treatment groups: 1) HCQ (200 mg, twice daily for four weeks), 2) clarithromycin (500 mg, twice daily for four weeks), and 3) a control group receiving a placebo (similar to the last two groups). The patients were randomly assigned to the groups using a computer-generated random number list generated by an independent statistician. Demographic data and clinical information, including disease-related events, pre-existing conditions, imaging results, treatment regimens, and follow-ups, were collected.

A common method used in similar studies was employed to express the results of the patient's CT scans. In this method, both lungs are divided into 20 regions based on 18 anatomical segments, and the level of opacity is scored on a scale of 0-2, with 0 representing the absence of pulmonary involvement, 1 the involvement of less than 50% of the area, and 2 the involvement of more than 50% of the lungs. The intensity of the involvement was quantitatively reported for each patient (13).

Patients were followed up two and four weeks after starting the treatment. The evaluation was performed in a single-blind manner, with the physician being unaware of the patient's group assignment. At the end of the fourth week, shortness of breath, cough, laboratory tests, the 6-min walk (6MW) test, and spirometry were re-evaluated for each patient. The findings were then compared in the groups.

3.3. Statistical Analysis

Statistical analysis was performed using the SPSS software (version 24, SPSS Inc., Chicago, IL, USA). Demographic characteristics and laboratory findings of the calculated median and interquartile range were compared in the groups using the Mann-Whitney U test. Categorical variables were analyzed using the Chi-squared or Fisher's exact test. The Kruskal-Wallis test was used to determine differences among the three groups of patients. The standardized mean difference (SMD) was calculated by dividing mean differences by their respective standard deviations and was used to compare results between groups. The Chi-squared test or Fisher's exact test was used to analyze the distribution of clinical data among three categories of patients. A P-value of <0.05 was considered statistically significant for all tests.

4. Results

A total of 34 participants were divided into three groups: HCQ (n=12), clarithromycin (n=11), and control/placebo (n=11). Detailed demographic characteristics of COVID-19 patients are shown in Table 1. Fever and cough were the most common clinical manifestations among all patients, as shown in Figure 1.

According to Table 2, after the treatment, a decrease was observed in VAS for cough in all three groups, but this amount was lower in the placebo group, compared to the other groups. The HCQ group had a higher VAS-based cough score (0.74±1.11) than the clarithromycin group, indicating that clarithromycin was more effective in improving cough (SMD=0.67, 95% CI [-0.18, 1.50]). Clarithromycin was also found to be more effective than placebo in reducing cough (SMD=-1.02, 95% CI [-1.90, -0.11]); however, it was not statistically significant (P=0.080).

Forced vital capacity (FVC) values of all three groups were normal before the treatment and increased slightly after the treatment. The FVC increase was higher in the HCQ group than in the clarithromycin group. The Forced Expiratory Volume 1 (FEV1) increased equally in all three groups after the treatment, with no differences observed. The FEV1/FVC and Mid Expiratory Flow Rates25-75 (MEF25-75) values were normal in all three groups before the treatment and increased after the treatment, with the clarithromycin group showing a higher value, compared to the HCQ groups (SMD=-0.46, 95% CI [-1.29, 0.37]). The 6MW values of the clarithromycin and HCQ groups were in the low range (25%) before the treatment, while they were in the average range (75%-25%) in the placebo group. After the treatment, the 6MW value of all three groups increased and was placed in the average range. The clarithromycin group showed a higher increase, compared to the HCQ group (SMD=-0.65, 95% CI [-1.48, 0.20]).

The white blood cell (WBC) levels of all three groups were normal before and after the treatment, with a decrease in all three groups. The erythrocyte sedimentation rate (ESR) levels decreased after the treatment in all three groups but remained in the normal range, showing the low effectiveness of medications in reducing ESR, compared to the

Table 1. Demographic characteristics of patients

Variable	HCQ[1] (n=12)	Clarithromycin (n=11)	Placebo (n=11)
Gender: n (%)			
Male	6 (50.0)	7 (63.6)	9 (81.8)
Female	6 (50.0)	4 (36.4)	2 (18.2)
Age: Mean (SD) (year)	46.5 (7)	47 (10)	48 (9)
Background disease: n (%)			
Diabetes mellitus	0 (0.0)	2 (18.2)	2 (18.2)
Hypertension	0 (0.0)	2 (18.2)	3 (27.3)
Malignancy	0 (0.0)	0 (0.0)	1 (9.1)
Autoimmunity	0 (0.0)	1 (9.1)	0 (0.0)
Smoking: n (%)	1 (8.3)	3 (27.3)	0 (0.0)
Early symptoms: n (%)			
Fever	9 (75.0)	8 (72.7)	11 (100.0)
Body pain	7 (58.3)	9 (81.8)	9 (81.8)
Dyspnea	8 (66.7)	10 (90.9)	7 (63.6)
Cough	11 (91.7)	9 (81.8)	8 (72.7)
Myalgia	7 (58.3)	7 (63.6)	7 (63.6)
Anorexia	6 (50.0)	5 (45.5)	5 (45.5)
Gastrointestinal symptoms	6 (50.0)	3 (27.3)	2 (18.2)
Dyssomnia	2 (16.7)	3 (27.3)	2 (18.2)
Medications received in hospital: n (%)			
Azithromycin	8 (66.7)	6 (54.5)	3 (27.3)
Dexamethasone	5 (41.7)	5 (45.5)	7 (63.6)
HCQ	7 (58.3)	7 (63.6)	3 (37.3)
Sofosbuvir	1 (8.3)	2 (18.2)	2 (18.2)
Favipiravir	0 (0.0)	1 (9.1)	3 (27.3)
Lopinavir and Ritonavir	7 (58.3)	7 (63.6)	5 (45.5)
Atazanavir and Ritonavir	0 (0.0)	1 (9.1)	0 (0.0)
Linezolid	1 (8.3)	2 (18.2)	0 (0.0)
Remdesivir	1 (8.3)	1 (9.1)	2 (18.2)
Enoxaparin	4 (33.3)	4 (36.4)	1 (9.1)
Heparin	2 (16.7)	4 (36.4)	5 (45.5)
Interferon	1 (8.3)	2 (18.2)	6 (54.5)
Naproxen	3 (25.0)	5 (45.5)	2 (18.2)
Meropenem	5 (41.7)	7 (63.6)	5 (45.5)
Vancomycin	2 (16.7)	3 (27.3)	3 (27.3)
Plasma pheresis	1 (8.3)	0 (0.0)	2 (18.2)
Intravenous immune globulin	0 (0.0)	2 (18.2)	0 (0.0)
PCR[2] test	4 (33.3)	3 (27.3)	6 (54.5)

1. Hydroxychloroquine
2. Polymerase chain reaction

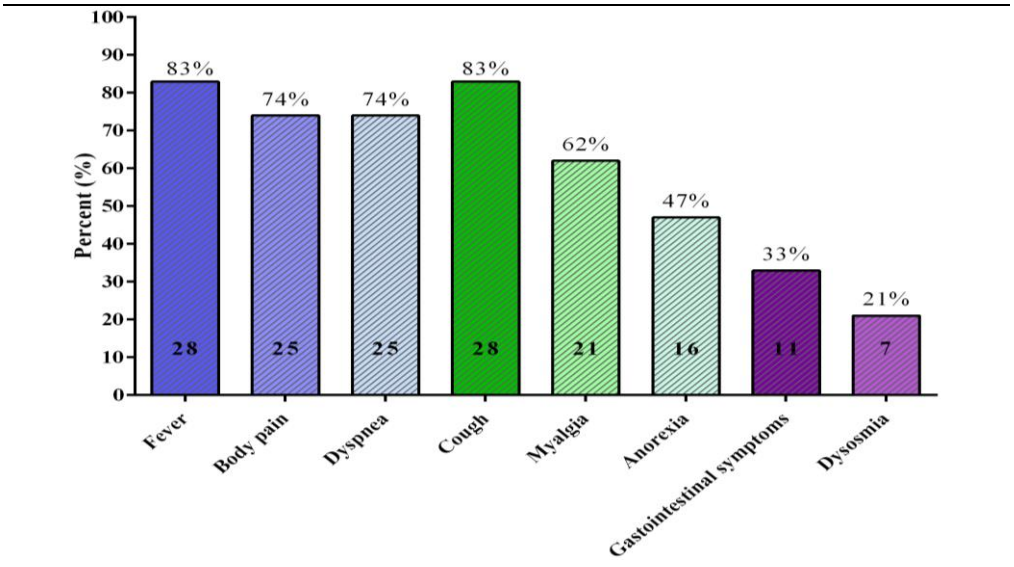

Figure 1. Clinical manifestations in patients with COVID-19 in the acute phase

placebo. The C-reactive protein (CRP) and lactate dehydrogenase (LDH) levels were normal before the treatment and decreased after the treatment in the normal range, showing the low efficacy of

medications in reducing CRP and LDH.

The evaluation of the effectiveness of medication on shortness of breath showed that patients receiving HCQ had a 64% chance of reducing shortness of breath, compared to the placebo group (RR=0.36), indicating moderate efficacy. Patients receiving clarithromycin had a 40% lower chance of having shortness of breath, compared to the placebo group (RR=0.60), indicating poor efficacy, with HCQ being more effective in reducing shortness of breath. A detailed comparison of quantitative variables after the treatment in three groups is represented in Table 2.

Table 3 showed no significant relationship between patients' initial clinical characteristics and shortness of breath after recovery. However, the majority of patients with minimal lung involvement in the acute phase (Medical Research Council [MRC] class 0 and 1) reported shortness of breath after the treatment. There was a significant correlation (P=0.050) between the severity of lung involvement and shortness of breath.

Table 4 shows that patients with less lung involvement had higher levels of FVC, compared to those with more lung involvement, with a difference of (17.36%, 95% CI [6.43, 28.29]). This strong relationship between lung involvement and FVC levels was statistically significant (P=0.003). Similarly, patients with less lung involvement had higher levels of FEV1 with a difference of (14.23%,

Table 2. Comparison of quantitative variables after treatment in three groups after controlling the effect of baseline

Variable	Group1 HCQ Mean (SD[1])	Group 2 Clarithromycin Mean (SD)	Group 3 Placebo Mean (SD)	Comparison 1 (group 1 vs. 2) group1–group2			Comparison 2 (group 1 vs. 3) group1–group3			Comparison 3 (group 2 vs. 3) group2–group3		
				MD[2] (95% CI[3])	SMD[4] (95% CI)	P-value	MD (95% CI)	SMD (95% CI)	P	MD (95% CI)	SMD (95% CI)	P-value
VAS[5] cough	0.76 (1.11)	0.02 (1.10)	1.15 (1.12)	0.74 (-0.44, 1.92)	0.67 (-0.18, 1.50)	0.29	-0.38 (-1.60, 0.83)	-0.35 (-1.17, 0.47)	0.72	-1.12 (-2.35, 0.10)	-1.02 (-1.90, -0.11)	0.08
FVC[6]%	80.81 (9.47)	78.34 (9.50)	81.32 (9.38)	2.47 (-7.85, 12.79)	0.26 (-0.56, 1.08)	0.83	-0.51 (-10.63, 9.61)	-0.05 (-0.87, 0.76)	0.99	-2.97 (-13.35, 7.41)	-0.32 (-1.15, 0.53)	0.76
FEV[7]-1%	90.47 (8.57)	90.57 (8.68)	90.47 (8.48)	-0.10 (-9.53, 9.33)	-0.01 (-0.83, 0.81)	1.00	0.00 (-9.11, 9.12)	0.00 (-0.82, 0.82)	1.00	0.10 (-9.39, 9.59)	0.01 (-0.82, 0.85)	1.00
FEV-1/FVC	92.63 (3.13)	94.08 (3.11)	91.41 (3.12)	-1.45 (-4.81, 1.90)	-0.46 (-1.29, 0.37)	0.55	1.22 (-2.15, 4.59)	0.39 (-0.44, 1.21)	0.65	2.67 (-0.74, 6.08)	0.86 (-0.03, 1.66)	0.15
MEF[8]25-75%	113.81 (16.58)	121.58 (17.23)	113.45 (17.14)	-7.77 (-26.02, 10.48)	-0.46 (-1.28, 0.37)	0.55	0.36 (-17.73, 18.45)	0.02 (-0.80, 0.84)	0.99	8.13 (-11.38, 27.64)	0.47 (-0.38, 1.31)	0.57
6MW[9] (meter)	583.77 (78.31)	635.88 (82.55)	585.46 (80.59)	-52.11 (-139.86, 35.64)	-0.65 (-1.48, 0.20)	0.32	-1.68 (-86.26, 82.89)	-0.02 (-0.84, 0.80)	0.99	50.43 (-42.71, 143.56)	0.62 (-0.25, 1.47)	0.39
WBC	5950.92 (964.82)	6469.34 (973.2)	6166.02 (942.83)	-518.42 (-1587.68, 550.84)	-0.53 (-1.36, 0.30)	0.47	-215.10 (-1236.82, 806.63)	-0.22 (-1.04, 0.60)	0.86	303.32 (-752.52, 1359.16)	0.32 (-0.53, 1.15)	0.76
Diff% segment	62.51 (5.17)	61.56 (5.19)	59.93 (5.20)	0.95 (-4.61, 6.51)	0.18 (-0.64, 1.00)	0.91	2.57 (-3.01, 8.16)	0.50 (-0.34, 1.32)	0.50	1.63 (-4.11, 8.16)	0.31 (-0.53, 1.15)	0.77
Diff %lymphocyte	31.35 (4.40)	30.83 (4.37)	33.91 (4.40)	0.52 (-4.19, 5.23)	0.12 (-0.70, 0.94)	0.96	-2.55 (-7.31, 2.21)	-0.58 (-1.41, 0.26)	0.40	-3.07 (-7.89, 1.75)	-0.70 (-1.56, 0.17)	0.27
ESR[10]	10.12 (5.40)	9.11 (5.44)	8.31 (5.41)	1.01 (-4.85, 6.86)	0.19 (-0.64, 1.00)	0.91	1.81 (-3.98, 7.61)	0.33 (-0.49, 1.16)	0.73	0.80 (-5.18, 6.79)	0.15 (-0.69, 0.98)	0.94
CRP[11]	3.85 (0.47)	4.12 (0.47)	4.03 (0.47)	-0.27 (-0.77, 0.23)	-0.57 (-1.40, 0.27)	0.40	-0.18 (-0.68, 0.32)	-0.38 (-1.20, 0.45)	0.66	0.09 (-0.42, 0.60)	0.19 (-0.65, 1.03)	0.90
LDH[12]	286.16 (89.51)	293.96 (89.39)	286.78 (88.11)	-7.80 (-105.38, 89.78)	-0.09 (-0.73, 0.90)	0.98	-0.62 (-96.19, 94.95)	-0.01 (-0.83, 0.81)	1.00	7.17 (-90.15, 104.50)	0.08 (-0.76, 0.92)	0.98

1. Standard deviation
2. Mean deviation
3. Confidence interval
4. Standardized Mean difference
5. Visual analog scale
6. Forced vital capacity
9. Forced Expiratory Volume
10. Mid-Expiratory Flow Rates
11. 6-Min Walk Test
12. Erythrocyte Sedimentation Rate

Table 3. Comparison of shortness of breath after the treatment and the clinical features of patients

MRC[1] Variable	Class 0 (n=16)	Class 1 (n=8)	Class 2 (n=7)	Class 3 (n=3)	P-value
Days of hospitalization: n (%)					
<10 days	8 (50.0)	6 (75.0)	1 (14.3)	2 (66.7)	
10<days<20	6 (37.5)	1 (12.5)	4 (57.1)	1 (33.3)	0.37
>20 days	2 (12.5)	1 (12.5)	2 (28.6)	0 (0.0)	
Medications received in hospital: n (%)					
Azithromycin	8 (50.0)	5 (62.5)	3 (42.9)	1 (33.3)	0.81
Dexamethasone	7 (43.7)	4 (50.0)	4 (57.1)	2 (66.7)	0.87
HCQ	9 (56.3)	3 (37.5)	4 (57.1)	1 (33.3)	0.75
Sofosbuvir	2 (12.5)	1 (12.5)	1 (14.3)	1 (33.3)	0.82
Favipiravir	3 (18.7)	0 (0.0)	0 (0.0)	1 (33.3)	0.25
Lopinavir and Ritonavir	9 (56.3)	4 (50.0)	4 (57.1)	2 (66.7)	0.97
Atazanavir and Ritonavir	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.76
Linezolid	2 (12.5)	0 (0.0)	1 (14.3)	0 (0.0)	0.66
Remdesivir	2 (12.5)	0 (0.0)	2 (28.6)	0 (0.0)	0.34
Enoxaparin	5 (31.3)	0 (0.0)	4 (57.1)	0 (0.0)	0.06
Heparin	5 (31.3)	3 (37.5)	1 (14.3)	2 (66.7)	0.43
Interferon	4 (25.0)	1 (12.5)	3 (42.9)	1 (33.3)	0.60
Naproxen	5 (31.3)	3 (37.5)	2 (28.6)	0 (0.0)	0.67
Meropenem	9 (56.3)	2 (25.0)	4 (57.1)	2 (66.7)	0.44
Vancomycin	3 (18.7)	1 (12.5)	2 (28.6)	2 (66.7)	0.27
Plasma pheresis	1 (6.3)	0 (0.0)	2 (28.6)	0 (0.0)	0.2
Intravenous immune globulin	1 (6.3)	0 (0.0)	1 (14.3)	0 (0.0)	0.66
Age: n (%)					
20-40 year	2 (12.5)	1 (12.5)	3 (42.9)	0 (0.0)	0.25
40-60 year	14 (87.5)	7 (87.5)	4 (57.1)	3 (100.0)	
Gender: n (%)					
Male	12 (75.0)	4 (50.0)	4 (57.1)	2 (66.7)	0.64
Female	4 (25.0)	4 (50.0)	3 (42.9)	1 (33.3)	
CT[2] scan: n (%)					
Mild	7 (43.7)	8 (100.0)	3 (42.9)	2 (66.7)	0.05*
Sever	9 (56.3)	0 (0.0)	4 (57.1)	1 (33.3)	
Days between symptoms to refer: n (%)					
<2 months	9 (56.3)	6 (75.0)	1 (14.3)	1 (33.3)	0.10
>2 months	7 (43.7)	2 (25.0)	6 (85.7)	2 (66.7)	

1. Medical Research Council
2. Computerized tomography

95% CI [3.06, 25.40]), indicating a statistically significant relationship between lung involvement and FEV1 levels (P=0.010). However, there was no significant correlation found between FEV1/FVC, 6MW, and MEF25-75 with the initial CT scan score.

Ultimately, the effectiveness of the treatment in each group was evaluated and compared to their acute phase of the disease. The changes in cough (VAS) in the HCQ group showed a significant correlation with hospitalization days (P=0.020), with patients hospitalized for less than 10 days having a 51% greater reduction in VAS, compared to those hospitalized for more than 10 days. There was a weak, non-significant correlation between the number of hospitalization days and decreased cough VAS in the clarithromycin and placebo groups. In the HCQ and clarithromycin groups, age had a non-significant correlation with decreased VAS, while there was no correlation in the placebo group. Patients under 50 years responded better to medications and experienced reduced cough VAS. Early clinic visits (within 2 months of symptom onset) had a significant correlation with decreased VAS in the HCQ group (P=0.009), but not in the clarithromycin group. Low lung involvement was also correlated with decreased VAS in the HCQ group, while a weak correlation was observed in the other two groups.

Table 5 provides details on cough VAS and patients' characteristics during the treatment.

Table 4. Comparison of spirometry and 6-min walk with initial CT scan of patients

Variable	CT mild (n=20) Mean (SD)	CT sever (n=14) Mean (SD)	MD (95% CI)	SMD (95% CI)	P-value
FVC%	87.52 (13.80)	70.16 (17.46)	17.36 (6.43, 28.29)	1.13 (0.38, 1.86)	0.003*
FEV1%	93.32 (13.65)	79.09 (18.37)	14.23 (3.06, 25.40)	0.90 (0.18, 1.61)	0.01*
FEV1/FVC	89.33 (6.61)	92.34 (5.48)	-3.01 (-7.40, 1.37)	-0.49 (-1.18, 0.21)	0.17
MEF25-75%	104.23 (22.92)	110.44 (26.35)	-6.21 (-23.50, 11.09)	-0.25 (-0.94, 0.43)	0.47
6MW(meter)	522.35 (119.04)	514.86 (133.81)	7.49 (-81.41, 96.39)	0.06 (-0.62, 0.74)	0.86

Table 5. Correlation between the cough VAS during the treatment and the clinical characteristics of patients at the time of hospitalization

Variable	HCQ (n=12)			Clarithromycin (n=11)			Placebo (n=11)		
	MD (95% CI)	SMD (95% CI)	P-value	MD (95% CI)	SMD (95% CI)	P-value	MD (95% CI)	SMD (95% CI)	P-value
Days of hospitalization									
<10 days	-50.90 (-95.73, -8.07)	-1.55 (-2.84, -0.19)	0.02*	-25 (-93.49, 43.49)	-0.5 (-1.69, 0.72)	0.43	1.31 (-61.15, 63.77)	0.03 (-1.20, 1.26)	0.96
>10 days									
Age									
<50 year	-45.23 (-92.58, 2.12)	-1.25 (-2.49, 0.05)	0.06	-48.33 (-109.30, 12.64)	-1.09 (-2.35, 0.22)	0.11	-7.94 (-68.00, 52.12)	-0.18 (-1.37, 1.01)	0.77
>50 year									
Days between symptoms to refer									
<2 months	-60.41 (-102.27, -18.55)	-1.97 (-3.41, -0.47)	0.009*	-11.67 (-82.16, 58.82)	-0.23 (-1.41, 0.97)	0.72	-36.67 (-92.69, 19.35)	-0.93 (-2.20, 0.39)	0.17
>2 months									
CT Scan									
Mild	-35.18 (-95.25, 24.89)	-0.87 (-2.21, 0.51)	0.22	-25.00 (-93.49, 43.49)	-0.50 (-1.69, 0.72)	0.43	-1.84 (-62.18, 58.50)	-0.04 (-1.23, 1.15)	0.95
Sever									
ESR									
<42	-45.23 (-92.58, 2.12)	-1.25 (-2.49, 0.05)	0.06	39.17 (-25.43, 103.77)	0.83 (-0.44, 2.05)	0.20	-27.5 (-84.18, 29.18)	-0.66 (-1.87, 0.58)	0.30
>42									
CRP									
<6	5.24 (-51.72, 62.20)	0.12 (-1.03, 1.27)	0.84	21.43 (-50.30, 93.16)	0.42 (-0.83, 1.66)	0.52	15.28 (-43.97, 74.53)	0.35 (-0.85, 1.54)	0.57
>6									
LDH									
<645	-11.91 (-68.37, 44.55)	-0.27 (-1.42, 0.88)	0.65	-38.54 (-112.45, 35.37)	-0.80 (-2.15, 0.60)	0.27	-1.31 (-63.78, 61.16)	-0.03 (-1.26, 1.20)	0.96
>645									

5. Discussion

This study was conducted to evaluate the treatment of patients with residual respiratory symptoms after recovering from the acute phase of COVID-19. The patients were divided into three groups, treated with HCQ, clarithromycin, and a placebo, to cure prolonged cough and shortness of breath. It was found that clarithromycin was more effective in improving prolonged cough, while HCQ was more effective in improving prolonged shortness of breath. A detailed analysis showed that HCQ was more effective in improving cough in patients under 50 years, with shorter hospitalization periods, and shorter intervals between visiting the clinic and the onset of symptoms.

Studies have revealed that a significant number of COVID-19 patients (13%-96%) experience persistent symptoms even after recovering from the acute phase of the disease (14, 15). According to recent research in Italy, only 15% of COVID-19 patients were completely symptom-free two months after the onset of their symptoms, while half of them experienced at least three symptoms. (16). Another study on 277 patients confirmed that half of them still had persistent symptoms three months after the onset of their illness. (17) Regarding lung dysfunction, a recent study reported that more than 60% of individuals with COVID-19 reported persistent symptoms with radiologic abnormalities three months after discharge (18). Such studies have been performed to evaluate the prognosis of long-term lung involvement in other family members of the virus. One study on 94 patients with SARS one year after initial recovery showed that only 63% had a completely normal pulmonary function, while the rest experienced varying degrees of decrease in their FEV1/FVC and DLCO. (17)

These studies highlight the need for ongoing monitoring and management of COVID-19 patients in the recovery phase to address long-term lung involvement and other symptoms.

Despite reports of abnormal lung function and radiological findings in discharged COVID-19 patients, the long-term effects of the disease have not been thoroughly studied, leaving many aspects unknown. Therefore, understanding the long-term effects of COVID-19 is crucial (16, 19, 20). The most concerning issue is the potential development of pulmonary fibrosis after recovery from the acute phase of the disease, which is believed to result from virus-induced damage, the immune response, and the immune system's attempts to repair residual damage (21). Interstitial pneumonia is the most common manifestation of the acute phase of the disease, which usually recovers within 3-6 weeks (22). However, it remains unclear which patients are more likely to experience complications after recovery. A study in Saudi Arabia found that age of over 50 years and pre-existing comorbidities

are associated with prolonged post-COVID symptoms, but there was no correlation between gender and the severity of initial symptoms (23).

The hypothesis is that controlling residual inflammation during the recovery phase of COVID-19 can prevent the progression to fibrosis. Studies have shown the effectiveness of corticosteroids and pulmonary rehabilitation, and the present study utilized the immunomodulatory effects of HCQ and clarithromycin to control residual inflammation.

The mechanisms behind macrolides as anti-inflammatory treatments for chronic lung diseases are not well understood. Nonetheless, it has been shown that they can inhibit the activity of nuclear factor kappaB (NF-κB), a transcription factor that triggers the expression of pro-inflammatory genes, such as tumor necrosis factor-alpha (TNF-α), interleukin 8 (IL-8), and IL-1beta (24). Studies indicate that macrolides can reduce the production of pro-inflammatory cytokines and chemokines, such as TNF-α, sTNFR1, sTNFR2, IL-1b, IL-6, IL-8, IL-10, IP-10, and CCL18, by alveolar macrophages in various lung disorders, including bronchiectasis, cystic fibrosis, chronic obstructive pulmonary disease (COPD), and bronchiolitis obliterans organizing pneumonia (24-26). At the start of the COVID-19 pandemic, clarithromycin and azithromycin were thought to be good options for treatment because they could inhibit the production of many cytokines and chemokines. However, subsequent research showed that clarithromycin was more effective due to its higher activity, better gastric acid resistance, and improved bioavailability than azithromycin. This may be related to its stronger inhibition of NF-κB activation (27). The reason why clarithromycin acts as a stronger immunomodulator than azithromycin may be related to NF-κB activation (28). Therefore, we chose clarithromycin as the best macrolide to try in the recovery phase of COVID-19. Our results showed that clarithromycin effectively controlled symptoms of pneumonia, especially coughing, during the recovery phase. It is noteworthy that the drug was even more effective in cases with a history of severe acute-phase inflammation, compared to milder cases.

Another medication used for the treatment of COVID-19 is HCQ (29). This anti-malarial medicine, also used in rheumatic diseases, is presumed to have immunological effects. By increasing endosomal pH, it inhibits pH-dependent steps of the replication of several viruses. Furthermore, HCQ can inhibit the production of pro-inflammatory cytokines, such as IL-1 and TNF-α (30). Besides, this medicine is effective in controlling innate immune responses by interfering with TLR signaling (31). According to all the previously mentioned immunomodulatory mechanisms, the use of medication can be effective not only to control the cytokine storm in the acute phase but also to reduce the inflammation remaining in the recovery phase. This medication has been used successfully in the treatment of interstitial pulmonary diseases in children (32).

The efficacy of clarithromycin and HCQ in alleviating symptoms of post-acute COVID-19 was previously studied. The results showed that HCQ was particularly effective in managing respiratory symptoms in the recovery phase, especially for patients with mild inflammation during the acute phase. Lung involvement was evaluated through CT scans and pulmonary function tests, including spirometry and 6MW tests. The findings also revealed a strong correlation between lung involvement score, as well as FVC and FEV1 levels, with patients with less lung involvement showing higher FVC and FEV1 values. Therefore, a simple spirometry test can serve as a reliable and non-invasive method for monitoring lung status during the recovery phase, rather than relying on multiple CT scans.

The comparison of clarithromycin and HCQ in the treatment of post-acute COVID-19 showed contrasting results. Clarithromycin was more effective in reducing cough, as measured by the VAS, but further analysis revealed that HCQ was more effective in reducing cough in patients with less severe acute-phase symptoms. Patients with shorter hospital stays, younger age, lower lung involvement on CT scans, and quicker referral times after the initial symptoms had better responses to HCQ treatment. Similar results were found when comparing the laboratory parameters of patients, such as ESR.

We compared the effects of clarithromycin and HCQ on individuals with post-acute COVID-19 syndrome and found that patients with an ESR of >42 (at admission) had a better response to clarithromycin in reducing cough severity. On the other hand, HCQ was more effective in reducing cough severity in patients with an ESR of <42. Additionally, HCQ had a 65% chance of reducing shortness of breath, compared to the placebo group. There was a significant correlation between the level of lung involvement in CT scans and the reduction of shortness of breath after four weeks of intervention and follow-up, with a moderate correlation in the HCQ group and a weak negative correlation in the clarithromycin group. Our findings suggest that clarithromycin is more effective in reducing the levels of remaining mediators (such as IL-2, IL-7, IL-10, GSCF, IP10, MCP1, MIP1A, and TNF-α) in the recovery phase, especially in severe cases with higher levels of these mediators (33).

The effects of clarithromycin and HCQ on lung function tests were compared in individuals with post-acute COVID-19. Results showed that clarithromycin had a greater impact on improving lung function, as the amount of FEV1, FVC, MEF2575, and 6MW increased more in the group receiving clarithromycin, compared to the other two groups.

Some articles have stated the beneficial effect of corticosteroids in the treatment of patients with prolonged interstitial lung involvement in the recovery phase of COVID-19 (34). However, the use of steroids has always been associated with major concerns due to many side effects. These findings in this article could be valuable for future treatment strategies, but further research with larger sample sizes is needed to support these results. Since the results of this study were not statistically significant due to the limited number of samples, it is suggested to conduct more comprehensive studies in the future. Additionally, while clarithromycin and HCQ were evaluated separately in this study, it is possible that the combination of the two drugs may be more effective in treating post-COVID-19 symptoms. Some studies have reported successful recovery of COVID-19 pulmonary dysfunction with a significant reduction in viral load in patients who received a combination of clarithromycin and HCQ (35-37).

6. Conclusion

Our study demonstrated that a significant number of COVID-19 patients experience lingering symptoms in the post-acute phase. Despite the recent emergence of the COVID-19 pandemic, the long-term effects of the disease are yet unknown, but the possibility of secondary fibrosis due to persistent inflammation in lung involvement is a serious concern. The use of immunomodulatory medications, in conjunction with corticosteroids, to manage symptoms appears to be a rational approach. Our results did not reveal a marked difference between HCQ and clarithromycin in terms of efficacy. A major limitation of our study was the small sample size, as it was conducted in a single center and limited resources hindered our ability to follow up with all discharged patients. Further evaluation of these medications with larger sample sizes and the exploration of the effects of other therapeutic agents for post-COVID-19 syndrome is recommended.

Acknowledgments

Our study was conducted in accordance with the ethical guidelines established by the Iran University of Medical Sciences Ethical Committee (IR.IUMS.FMD.REC.1399.244) and was registered on the clinical trial site of Iran on 2020-08-11 with Trial ID IRCT20200718048129N1. We would like to express our gratitude to the Department of Allergy and Clinical Immunology at Rasoul Akram Hospital at Iran University of Medical Sciences, Tehran, Iran for their support in carrying out this study.

Footnotes

Conflicts of Interest: The authors declare they have no competing interests.

Authors' contributions: Sima Bahrami and Mohammad Hassan Bemanian are joint first authors and contributed equally to the present study. They collected data and drafted the manuscript. Saba Arshi, Mohammad Nabavi, Sima Shokri, Morteza Fallahpour, and Afshin Rezaeifar contributed in a consultant role and made critical suggestions to address. All authors read the final version of the manuscript, made relevant amendments, and approved the final version of the manuscript.

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Consent for publication: Each participant gave an informed written consent form.

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