Original Article

The Efficacy and Safety of Adding Chlorpromazine to Atazanavir/Ritonavir Regimen in the Treatment of Moderate COVID-19 Patients, a Randomized Double-blind Clinical Trial

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ABSTRACT

Background: According to COVID-19 mutation and no defined treatment, it is necessary to find effective treatment. Chlorpromazine, a phenothiazine antipsychotic drug, has been shown in animal studies to have antiviral effects by inhibiting clathrin-mediated endocytosis. The aim of this study was to evaluate the effectiveness of adding chlorpromazine to the atazanavir/ritonavir regimen in the treatment of moderate COVID-19 patients.

Methods: In this randomized double-blind clinical trial, sixty hospitalized patients with moderate COVID-19 confirmed by CT findings or polymerase chain reaction (PCR) were enrolled. All patients received atazanavir/ritonavir 300mg/100mg once daily. In two parallel groups, chlorpromazine 25 mg three times a day or a placebo was administered for up to 14 days. Complete blood count with differential, C-reactive protein (CRP), liver enzymes, and erythrocyte sedimentation rate was measured on days 1, 3, 5, 7, and 10. The primary outcome was the improvement of oxygen saturation and the secondary outcome was the duration of hospitalization and conversion of PCR test results.

Results: Oxygen saturation during the hospitalization was not different among the two groups. The mean duration of hospitalization in the chlorpromazine group was 7.4±2.7 days and in the placebo was 8.2±3 days (P=0.2). Compared to baseline, both groups showed an increase in white blood cell count (P=0.04) and polymorphonuclear cells (P=0.04) but lymphocyte count decreased. At the end of the study, the PCR test was negative in 100% of patients in the chlorpromazine group and 95% of patients in the placebo group.

Conclusion: In adult hospitalized patients with moderate symptomatic COVID-19, adding chlorpromazine to the atazanavir/ritonavir regimen did not improve outcomes.

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Introduction

The coronavirus disease 2019 (COVID-19) causes severe acute respiratory syndrome (SARS) in humans. It is caused by a novel coronavirus and originated in Wuhan, China in December 2019 and became a pandemic in the 21st century [1, 2]. Globally on March 2022, there have been 469,212,705 confirmed cases of COVID-19, including 6,077,252 deaths, reported to the World Health Organization (WHO) [3]. It is the third and the most serious coronavirus epidemic after SARS-CoV-1 in 2003 and MERS-CoV in 2012. The virus contains a very large RNA virus genome and in cryo-electron tomography, it has been revealed that it is spherical with an envelope [4, 5]. The first stages of infection with coronavirus are entry into human cells and replicating its genome to initiate and spread the infection [6, 7]. COVID-19 progression can be divided into three phases: The early infection phase involving viral replication and mild symptoms, pulmonary phase involving adaptive immunity stimulation and predominance of respiratory symptoms, and the hyperinflammation phase leading to conditions, such as acute respiratory disease syndrome (ARDS) [8, 9].

The treatment of patients with mild to moderate COVID-19 is of utmost importance because about 14% of patients progress to severe COVID-19 in only one week [10, 11]. The median time to critical COVID-19 appearance may be as early as eight days from the beginning of symptoms [12] and the median time to death from the symptom's onset is 16 days [13]. Therefore, it would be necessary to pharmacologically treat patients with mild to moderate COVID-19 who are at risk of progression to severe or critical disease.

Some antiviral drugs have shown efficacy against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in both in vitro and in vivo models [14, 15]. Atazanavir, an azapeptide oral protease inhibitor, was approved by the food and drug administration (FDA) in 2003 for HIV infection with a good safety profile [16].

In addition, Atazanavir decreases the levels of IL-6 and TNF-α in COVID-19-infected patients, an effect that was better than chloroquine, a compound recognized for its anti-viral and anti-inflammatory activities [17, 18]. Numerous studies have been initiated for out- and in-patients with COVID-19 to test atazanavir combined or not with other commercial drugs, such as ritonavir or dexamethasone; however, no definitive response has emerged from these studies.

Chlorpromazine synthesized in 1951 by Rhône Poulenc, has been used in psychiatry since 1952 when Jean Delay and Pierre Deniker, two psychiatrists at Sainte-Anne hospital, discovered its antipsychotic properties. According to Inoue et al., SARS-CoV (a coronavirus similar to SARS-CoV-2) uses clathrin-mediated endocytosis (CME) to enter the host cell [19]. Chlorpromazine, prescribed as an antipsychotic medication, inhibits the formation of clathrin-coated vesicles and can block CME [20]. On the other hand, chlorpromazine increases the intra-vesicular pH and because of its cationic amphiphilic properties, it can inhibit S protein activation [21]. According to animal studies, in mice, chlorpromazine increases the concentration of the anti-inflammatory cytokines, such as IL-10, and decreases the pro-inflammatory cytokines, like IL-6 and TNFα after administration of endotoxins [22]. Adverse effects of chlorpromazine are drowsiness, dry mouth, constipation, blurred vision, urine retention, orthostatic hypotension, and some uncommon adverse reactions, including QT prolongation and cardiac rhythm disorders [23-25]. These risks were limited by clinical daily monitoring at the hospital over the whole period of chlorpromazine treatment and the vital signs, laboratory tests, and also all complaints related to disease or chlorpromazine were recorded.

The aim of this study was to evaluate the role of chlorpromazine as an add-on therapy to the atazanavir/ritonavir regimen in the treatment of moderate COVID-19 patients. This hypothesis is mainly based on the activity of chlorpromazine against RNA viruses, like COVID-19 with established efficacy for in vitro studies [26-28].

Materials and Methods

Study design

This study was a pilot double-blind placebo-controlled randomized clinical trial. This study recruited patients from October 22, 2020, to January 7, 2021, at two educational hospitals of Mazandaran University of Medical Science, in the north of Iran. Written informed consent was obtained from all patients, or their legal representatives if they were unable to provide consent.

Sixty patients who had inclusion criteria entered the study after the goals of the study were explained. Patients were randomly assigned to one of the two parallel treatment groups using a block randomization method.

To keep the blindness, a computer-based 5-digit random code was assigned to each patient.

In this study, 169 patients were studied, of whom 60 patients met the inclusion criteria and were randomized with a 1:1 ratio to receive chlorpromazine (Tehran-Shimi Pharmaceutical Company, Iran, 25 mg) three times a day or the placebo. Both groups received atazanavir /ritonavir 300 mg/100 mg (Mylan Pharmaceutical Pvt, India) once a day for up to 14 days in the hospital.

The placebo was made in the Department of Pharmaceutics of the School of Pharmacy using Avicel (microcrystalline cellulose).

Inclusion criteria

Patients who had all of these criteria were included: 1) The age of 18-70 years, 2) Being diagnosed with COVID-19 according to clinical symptoms, confirmed by reverse transcription polymerase chain reaction (RT-PCR) or CT scan of the lungs, 3) Intend to receive atazanavir/ritonavir as antiviral regimen, 4) The SpO_2 of less than 94 mmHg (without oxygen), oral temperature >37.2 ˚C, respiratory rate (RR) >24/min, or having dyspnea.

Exclusion criteria

Patients who had each of these criteria were excluded: 1) Those who did not give informed consent; 2) Receiving antipsychotic medicines at present or during the last 14 days; 3) History of seizure, Parkinson's disease, or dementia; 4) Liver dysfunction; 5) History of pheochromocytoma; 6) Allergy to phenothiazine drugs; 7) Existence of any major drug interactions between the patient's routine medications and chlorpromazine; 8) Pregnancy or breastfeeding; 9) Previously treated for COVID-19 or enrolment in other trials.

Outcome measures

The primary outcome of the study was the improvement of SpO_2.

Secondary outcomes were the day of hospitalization, the need for ICU admission, lymphocyte count, and the rate of conversion of RT-PCR positive test to negative result. Initial PCR was performed for all patients. The next PCR was performed on the fifth or discharge day, whichever was earlier, and if positive, it was repeated a week later.

The complete blood count (CBC) and biochemical tests, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), C - reactive protein (CRP) as well as erythrocyte sedimentation rate (ESR) were conducted on days 1, 3, 5, 7, and 10. Oxygen saturation and respiratory rate (RR) were evaluated for all days of hospitalization. On all days of hospitalization, patients were evaluated for any potential side effects caused by chlorpromazine. If the side effects were bothersome or serious, patients were excluded from the study.

Statistical analysis

The normality of data was checked by Shapiro-Wilk Test. Independent sample t-test or Mann-Whitney U test was used for the comparison of continuous variables between the two groups. Wilcoxon matched-pair signed-rank test and chi-square test were used for the comparison of continuous variables and qualitative data before and after treatment, respectively. Repeated measures ANOVA was used to determine the changes of variables (e.g. laboratory data) on different days in each group.

The trend of changes in laboratory data and O_2 saturation was compared by the generalized estimating equation (GEE) model. SPSS software, version 26.0 was applied for statistical analysis.

Result

Patients

A total of sixty subjects were enrolled in this study, including the chlorpromazine group (n=30) and placebo group (n=30). Thirteen patients (ten patients in the CLPZ group and three patients in the placebo group) did not continue the study (Figure 1). Table 1 shows the baseline demographic and clinical characteristics of the 47 patients who completed the study. The mean age of patients was 52±12.74 years, and 28% of the patients were men. The most common presenting symptoms were fever (defined as temperature ≥37.8) (61.7%), dyspnea (53.2%), elevated CRP (50.23%), and cough (38.3%). All patients had lung injury on the first day and the mean percentage of their lung involvements was 48.9±14.65. The WBC counts were 5702±2437 cells/µL. On admission, lymphopenia (lymphocyte count <1500 cells/µL) was found in 33(70.2%) patients. On admission, patients had mild to moderate pneumonia as documented by clinical manifestations and CT findings. There were no between-group differences in baseline laboratory test results (e.g.

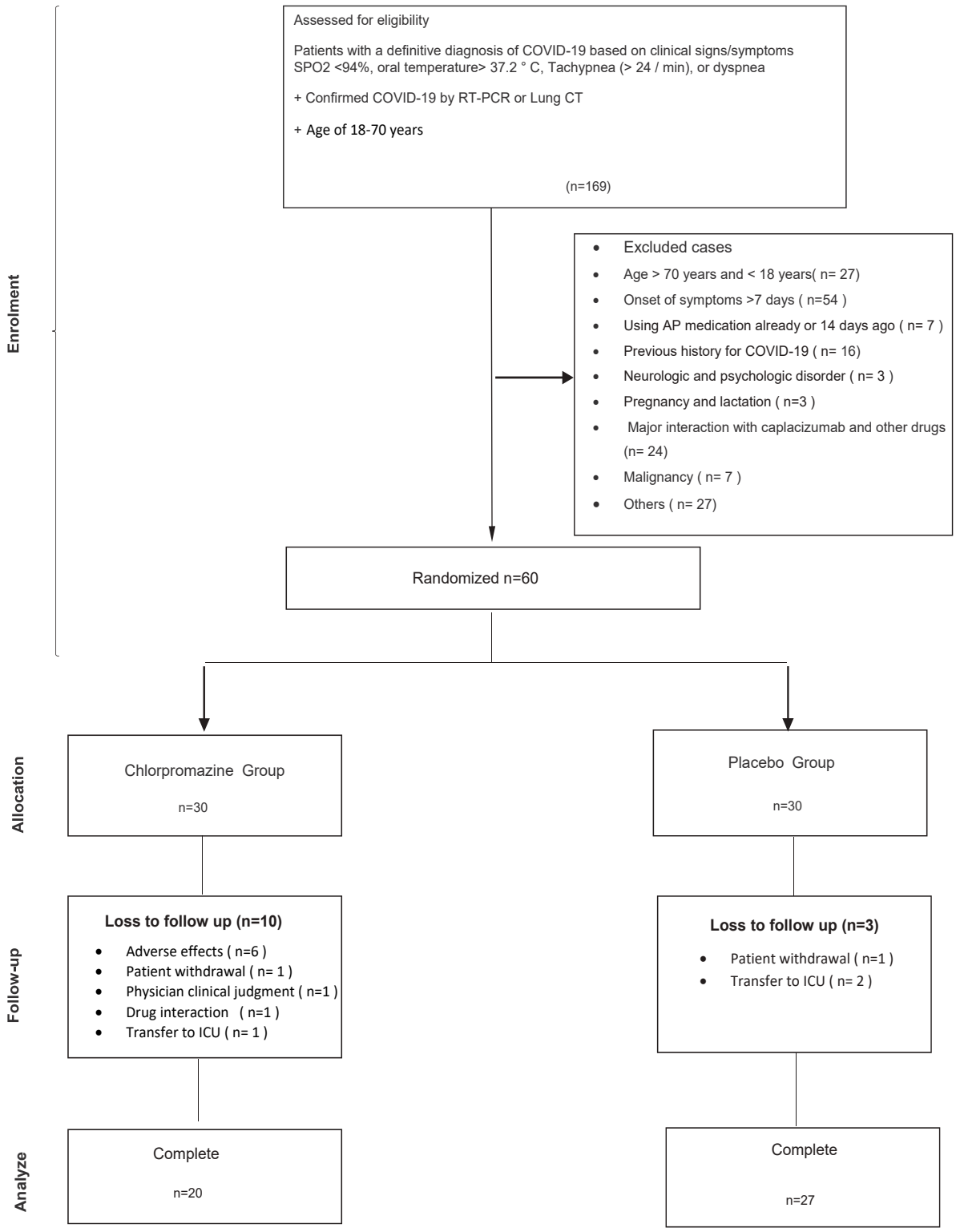

Figure 1. CONSORT flow chart

Table 1. Demographic and clinical characteristics of the patients at baseline

Characteristics		No. (%)/Mean±SD			P
		Total (n=47)	CLPZ Group (n=20)	Placebo Group (n=27)	
Age (y)		52±12.74	46.85±12.8	55.8±11.6	0.01
Male sex		28(59.6)	12(60)	16(59.3)	0.99
Coexisting conditions	Smoking	2(4.3)	1(5)	1(3.7)	0.99
	Diabetes	15(31.9)	5(25)	10(37)	0.52
	COPD	1(2.1)	0(0)	1(3.7)	0.99
	Asthma	1(2.1)	0(0)	1(3.7)	0.99
	HTN	14(29.8)	5(25)	9(33.3)	0.74
	CHD	4(8.5)	0(0)	4(14.8)	0.12
Symptoms	Fever (T> 37.8°C)	29(61.7)	10(50)	19(70.4)	0.22
	Cough	18(38.3)	9(45)	9(33.3)	0.54
	Dyspnea	25(53.2)	10(50)	15(55.6)	0.77
	Myalgia	22(46.8)	10(50)	12(44.4)	0.77
	Headache	15(31.9)	7(35)	8(29.6)	0.76
	Fatigue	22(46.8)	8(40)	14(51.9)	0.55
	Anorexia	17(36.2)	6(30)	11(40.7)	0.54
	Time onset symptoms	6.43±1.9	6.2±2.4	6.6±1.6	0.52
Physical examination[3]	Oral temperature (°C)	37.3±0.68	37.35±0.59	37.26±0.74	0.62
	Respiratory rate	18.23±1.02	18.45±0.83	18.1±1.14	0.22
	Heart rate	85.2±11.2	84.6±10.9	85.7±11.8	0.75
	SBP	118.85±16	117.25±13.42	120.04±17.75	0.56
	DBP	75.11±9.2	76±10.6	74.4±10.14	0.57
	% O_2 sat	93.62±2.8	93.7±3.01	93.56±2.65	0.86

CLPZ: Chlorpromazine.

CRP, WBC, and lymphocyte counts) and CT scores for lung lesions (Table 2).

Regarding the incidence of adverse effects, xerostomia was seen in five cases (16.6%) in the chlorpromazine group and one case (6.7%) in the placebo group. Somnolence occurred in ten cases (33.3%) of the chlorpromazine group and two cases of the placebo group. Dizziness was seen in four cases (13.3%) in the chlorpromazine group. Six patients from the drug group were excluded from the study due to intolerance to side effects, one case was due to xerostomia, three cases were due to somnolence, and the other two cases were due to somnolence and dizziness. The mortality rate in the chlorpromazine group was one case (3.3%) and in the placebo group, was two cases (6.7%) (Table 3).

Primary outcomes

There was no significant difference in oxygen saturation in the chlorpromazine group compared to the placebo group during the hospital stay.

Secondary outcome

Table 2. Patients' baseline laboratory test results

	Characteristics	Mean±SD			P
		Total (n=47)	ClPZ Group (n=20)	Placebo Group (n=27)	
Baseline lab test	Hemoglobin (mg/dL)	12.51±1.52	12.64±1.4	12.42±1.6	0.65
	WBC (µ/L)	5702.1±2437.3	5710±2580.9	5696.3±2375.4	0.98
	Lymphocyte (µ/L)	1282±581	1190±657	1353±518	0.35
	PMN (µ/L)	3954±1972	3806±1615	4051±2200	0.7
	Platelet (µ/L)	210.7±70.55	204.9±71.6	215.1±70.8	0.63
	BUN (mg/dL)	19.8±8.86	19±7.7	20.5±9.7	0.58
	Cr (mg/dL)	1.06±0.29	1.1±0.4	1.1±0.2	0.99
	AST (U/L)	31.9±11.47	29.8±11.6	33.4±11.4	0.32
	ALT (U/L)	33.9±22.41	32.8±25.4	34.7±20.5	0.78
	ALP (U/L)	162.7±62.34	154.9±61.5	168.5±63.7	0.49
	Na (mEq/L)	135.7±2.86	135.6±2.5	135.7±3.2	0.9
	K (mEq/L)	4.2±0.42	4.2±0.4	4.2±0.5	0.95
	Blood Sugar (mg/dL)	150.1±59.45	146.6±45.9	152.5±68.3	0.76
	ESR (mm)	46.9±22.19	43.3±24.8	49.6±20.2	0.36
	CRP (mg/L)	50.23±29.35	46.8±32.4	53.1±27.1	0.53
	CPK (U/L)	193.7±262.6	262±370.5	135.1±80.7	0.17
	LDH (U/L)	634.8±163.3	612.8±189.9	651.3±142.2	0.46
	Ferritin (mg/dL)	453.75±410.45	484.8±558	426.4±228.7	0.69
	PT (sec)	12.8±1.33	12.9±1.5	12.7±1.2	0.74
	INR	1.12±0.19	1.1±0.2	1.1±0.2	0.97
	Lung involvement (%)	44.9±14.65	46.8±15.5	43.3±14	0.45

CLPZ: Chlorpromazine.

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The duration of hospitalization in the chlorpromazine group (7.4±2.7) was almost 0.8 days less than the placebo group (8.2±3), but the difference was not significant (P=0.2). In the placebo group, an RT-PCR test was performed for all individuals; out of 22 people whose RT-RT-PCR test were positive (81.5%) on the day one of hospitalization, five (18.5%) patients had a positive PCR test on the seventh day, which represents a decrease of 77.3%. On the other hand, in the chlorpromazine group, an RT-PCR test was performed for all individuals; out of 14 people who had an RT-PCR positive test (70%) on the first day of hospitalization, two (10%) patients on the seventh day were RT-PCR-positive indicating an 85.7% decrease (Table 4). On the 14th day of hospitalization, none of the remaining 16 patients in the chlorpromazine group had a positive test (100% reduction) and in the placebo group, out of 20 patients, only one test was positive (95% reduction). The mean lymphocytes counts were 1190±657 cells/µL and 1353±518 cells/µL in the chlorpromazine and placebo groups on the first days of admission whereas they decreased to 1069±580 cells/µL and 1034±634 cells/µL after chlorpromazine and placebo treatments, respectively. The mean CRP levels on the first day for the placebo and chlorpromazine groups were 53.1±27.1 mg/dL and 46.8±24.8 mg/dL, which decreased to 44±30.2 mg/dL and 40.3±32.5 mg/

Table 3. Drugs used in the chlorpromazine and placebo groups

Drugs	No. (%)			P
	Total (n=47)	ClPZ Group (n=20)	Placebo Group (n=27)	
Remdesivir	12(25.5)	2(10)	10(37)	0.05
Lopinavir/ritonavir (Kaletra®)	1(2.1)	0(0)	1(3.7)	0.99
Daclatasvir/sofosbuvir (Sovodac®)	2(4.3)	2(10)	0(0)	0.18
Hydroxychloroquine	2(4.3)	2(10)	0(0)	0.17
Tocilizumab	1(2.1)	0(0)	1(3.7)	0.99
Interferon beta 1a (Recigen®)	23(48.9)	11(55)	12(44.4)	0.56
Antibiotic	41(89.1)	18(90)	23(88.5)	0.99
Ceftriaxone	39(83)	17(85)	22(81.5)	0.99
Meropenem	2(4.3)	2(10)	0(0)	0.18
Vancomycin;	1(2.1)	1(5)	0(0)	0.43
Azithromycin	7(14.9)	3(15)	4(14.8)	0.99
Corticosteroids	38(80.9)	16(80)	22(81.5)	0.99
Anticoagulant	45(95.7)	20(100)	25(92.6)	0.5

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Table 4. Primary and secondary outcomes in the chlorpromazine and placebo groups

Parameters		Mean±SD/No. (%)			P
		Total (n=47)	ClPZ Group (n=20)	Placebo Group (n=27)	
SpO_2		93.04±4.2	92.8±4.6	93.2±3.8	0.7
Days in hospital		7.8±2.8	7.4±2.7	8.2±3	0.2
PCR day 1	Positive	36(76.6)	14(70)	22(81.5)	0.65
	Negative	9(19.1)	5(25)	4(14.8)	
	Missied	2(4.3)	1(5)	1(3.7)	
PCR day 7	Positive	7(14.9)	2(10)	5(18.5)	0.67
	Negative	30(63.8)	14(70)	16(59.3)	
	Missied	10(21.3)	4(20)	6(22.2)	
PCR day 14	Positive	1(2.1)	0(0)	1(3.7)	0.59
	Negative	35(74.5)	16(80)	19(70.4)	
	Missied	11(23.4)	4(20)	7(25.9)	

CLPZ: Chlorpromazine.

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Table 5. Laboratory tests on days 1, 3, 5, and 10 of the treatment

Lab Tests	Day 1			Day 3			Day 5		
	CLPZ Group	Placebo Group	P Between Group	CLPZ Goup	Placebo Group	P Between Group	CLPZ Group	Placebo Group	P Between Group
WBC N Missed	5710±25 20 0	5696±2375 27 0	0.9	7836±3216 19 1	8561±3554 26 1	0.5	10492±3682 13 7	10033±362 21 6	0.58
Lymphocyte N Missed	1189±657 20 0	1353±517 26 1	0.2	918±415 19 1	1042±594 25 2	0.6	965±611 13 7	1096±780 20 7	0.85
PMN N Missed	3805±1615 17 3	4051±2200 26 1	0.86	6453±3094 19 1	7129±3590 26 1	0.47	9083±3465 13 7	8383±3370 21 6	0.5
PLT N Missed	204±71 20 0	215±70 27 0	0.63	241±83 19 1	267±90 26 1	0.6	304±103 13 7	309±125 21 6	0.99
ESR N Missed	43±24 18 2	49±20 24 3	0.27	48±21 16 4	58±25 24 3	0.16	38±19 13 7	55±22 17 10	0.04
CRP N Missed	46±32 16 4	53±27 19 8	0.54	46±38 15 5	50±33 18 9	0.6	17±14 9 11	25±28 13 14	0.84
CPK N Missed	262±370 18 2	135±80 21 6	0.73	240±435 16 4	136±153 19 8	0.9	143±213 13 7	82±57 16 11	0.65
LDH[3] N Missed	612±189 18 2	651±142 24 3	0.16	487±247 18 2	513±136 22 5	0.25	641±350 12 8	541±212 16 11	0.8
AST N Missed	29±11.5 18 2	33.4±11 25 2	0.3	33±25 18 2	34±20 27 0	0.73	34±23 13 7	49±39 21 6	0.3
ALT N Missed	32.7±25.3 18 2	34.7±20.5 25 2	0.43	37±26 18 2	36±19 27 0	0.7	55±43 12 8	34±23 21 6	0.57

Lab Tests	Day 7			Day 10			gEE Analysis			
	CLPZ Group	Placebo Group	P Between Group	CLPZ Group	Placebo Group	P Between Group	Total	CLPZ Group	Placebo Group	P
WBC N Missed	9500±4334 5 15	7977±2461 9 18	0.36	11700±424 2 18	8733±971 3 24	0.2	7442±3345	8028±3642	7676±3075	0.04
Lymphocyte N Missed	792±234 5 15	705±542 9 18	0.3	442±222 2 18	848±37 3 24	0.2	1051±607	1069±580	1034±634	0.67
PMN N Missed	7983±4060 5 15	6742±2843 9 18	0.36	10703±288 2 18	7397±956 3 24	0.2	6370±3305	6427±3554	6321±3097	0.04
PLT N Missed	314±115 5 15	305±125 9 18	0.99	313±37 2 18	214±50 3 24	0.2	252±104	234.6±98	267±107	0.69
ESR N Missed	44±23 5 15	38±19 8 18	0.62	30±15 2 18	40±25 4 23	0.8	50.7±2,1	52±24	49.5±19.6	0.21
CRP N Missed	20±18 4 16	30±33 7 20	0.93	14±6 2 18	22±27 4 23	0.99	42.2±3.2	40.3±3.5	44±30.2	0.2
CPK N Missed	171±76 4 16	114±136 8 19	0.15	166±43 2 18	77±75 4 23	0.27	183±353	266±48.5	103±7.6	0.6
LDH[3] N Missed	834±214 5 15	636±297 8 19	0.17	573±221 2 18	644±431 4 23	0.99	621±267	654±332	589±183.2	0.61
AST N Missed	38±30 5 15	44±29 10 17	0.59	18±6 2 18	22±11 4 23	0.8	38.7±28	37±26.4	39.9±29.4	0.1
ALT N Missed	61±44 5 15	59±30 10 17	0.86	33±14 2 18	45±14 4 23	0.27	45.3±3.3	46±35.2	45±32.1	0.09

dL after the treatment period, respectively. The median time from the onset of symptoms to enrolling in the trial was 6.43±1.9 days. The mean severity of lung involvement according to CT scan was 44.9±14.65% and the mean oxygen saturation on admission to the hospitalization was 93.62±2.8. The mean of ESR, CRP, CPK, and LDH levels in patients showed no significant difference between the two groups (Table 5).

Discussion

This randomized clinical trial found that adding chlorpromazine to the antiviral regimen of patients with moderate COVID-19 was not significantly effective on the SpO_2 or days of ICU or non-ICU stay.

Lymphocyte count is one of the most significant and consistent trends, suggesting that this indicator might reflect the disease progression, and lymphopenia is a predictor of prognosis in COVID-19 patients [26]. Patients with severe disease had more prominent laboratory abnormalities (including lymphopenia and elevated CRP) than those with non-severe disease [27]. Lymphopenia (lymphocytes <1500 per mm^3) is the most common lab finding in COVID-19 and is found in as many as 70% of the patients on admission. All patients had high CRP levels with an average of 50.23±29.35 on the first day of hospitalization.

This is the second clinical trial using chlorpromazine in patients with COVID-19, which was performed as a double-blind randomized study in two hospitals, while another study in France on chlorpromazine was a single-blind study [28].

Multiple drugs with in vitro antiviral activity against SARS-CoV-2 and/or immunomodulatory effects have been suggested to be clinically beneficial. In our study, atazanavir-ritonavir was prescribed as an antiviral regimen based on the national guideline regarding the treatment of COVID-19. Lymphopenia was observed in 70% of patients on admission, while lymphocyte counts showed no significant increase after 3, 5, 7, and 10 days of treatments to the normal range (P=0.67).

Elevated CRP levels (≥6 mg/dL) as positive CRP was observed in all patients on admission, while chlorpromazine could not significantly reduce CRP levels after 3, 5, 7, 10 days of treatment to the negative range and there was no statistically significant difference between the two groups according to changes in CRP during the treatment.

In a study conducted in 2014 to investigate the inhibitory effect of chlorpromazine on the Huh 7 cell line, the drug completely inhibited the proliferation of all seven cell lines at a dose of 12 µM. On the other hand, this study showed that the addition of chlorpromazine 1 hour prior to cell line infection led to a 2-log reduction of virus progeny titers, and the addition of chlorpromazine 1 hour after cell line infection reduced the virus by half to one log [29].

In a group of patients receiving the chlorpromazine, no life-threatening side effects were observed, and the annoying side effect in the patients was dry mouth.

In the treatment of HIV patients, atazanavir is a potent, well-tolerated, and effective once-daily protease inhibitor with a low pill burden [30]. A 96-week analysis suggested that the long-term efficacy of atazanavir/ritonavir monotherapy was inferior as compared to atazanavir/ritonavir plus two nucleosides reverse transcriptase inhibitors (NRTIs). Monotherapy was also associated with a lower incidence of adverse events [31].

Remdesivir demonstrated clinical benefit in a placebo-controlled trial in patients with severe COVID-19. However, its effect in patients with moderate disease who were randomized to a 10-day course of remdesivir, showed no statistically significant difference in clinical status (P=0.18 by Wilcoxon rank sum test) compared to standard care 11 days after treatment, but in a 5-day course, it showed a statistically significant difference (odds ratio, 1.65; 95% CI, 1.09-2.48; P=0.02) [32]. In this trial, atazanavir was considered the standard antiviral treatment for patients with moderate involvement, and in the case of disease progression or inadequate response, it was changed to another drug, including remedesivir, at the discretion of the clinician. According to the results, in the chlorpromazine group, fewer people (two vs. ten in the placebo group) needed to change their antiviral regimen to remdesivir (P=0.05).

Our study was designed according to our country's guidelines and hydroxychloroquine was ordered. Remdesivir was ordered for severe COVID-19 patients and availability of this drug was limited; thus, we used atazanavir as the primary antiviral.

Conclusion

Based on this study, adding chlorpromazine is not effective in the alleviation of clinical symptoms and modifying laboratory tests of moderate to severe COVID-19 in hospitalized patients that received atazanavir/ritunavir.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethics Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1399.617) and registered at the Iranian Clinical Trial Registration Database (IRCT) (No.: IRCT20200913048708N1).

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Authors' contributions

Conceptualization and supervision: David Darvishnia, Roya Ghasemian, Ahmad Alikhani and Jafar Akbari; Methodology: Nematollah Ahangar, Hamideh Abbaspour and Ebrahim Salehifar; Investigation, writing the paper, review & editing: All authors; Data analysis: Sima Ramezaninejad, Hamid Reza Namvar and Zahra Akbari.

Conflict of interest

The authors declared no conflicts of interest.

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