

Effect of Arbidol on COVID-19: A Randomized Controlled Trial

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Abstract

Background: The treatment of patients with COVID-19 included supportive care to relief the symptoms mainly. Although WHO mentioned there is not any effective treatments for COVID-19, but there is some reporting about the use of some antiviral drugs. The aim of current study is to determine the effect of Arbidol (ARB) on COVID-19 disease.

Methods: Using an open label randomized controlled trial, effectiveness of ARB on COVID-19 disease was conducted in a teaching hospital. One hundred eligible patients with diagnosis of Covid-19 recruited in the study and assigned randomly to two groups of either Hydroxychloroquine followed by Kaletra (Lopinavir-ritonavir) or Hydroxychloroquine followed by ARB. The primary outcome was hospitalization duration and clinical improvement 7 days after admission. The criteria of improvement were relief of cough, dyspnea and fever. Time to relieving fever was assessed across two groups too. Without any drop out, 100 patients were entered to final analysis with significant level of 0.05.

Results: The mean age of the patients was 56.6 (17.8) and 56.2 (14.8) in ARB and Kaletra groups respectively. Majority of patients were male across two groups (66% and 54%). The duration of hospitalization in ARB group was less than Kaletra arm significantly (7.2 versus 9.6 days; $P=0.02$). Time to relief fever was almost similar across two groups (2.7 versus 3.1 days in ARB and Kaletra arms respectively). Peripheral oxygen saturation rate was different after seven days of admission across two groups significantly (94% versus 92% in ARB and Kaletra groups respectively) ($P=0.02$). Based on multiple linear regression analysis, IHD, Na level and oxygen saturation at the time of admission and type of therapy were the independent adjusted variables that determined the duration of hospitalization in patients with COVID-19.

Conclusion: Our findings showed that Arbidol, compared to Kaletra, significantly contributes to clinical and laboratory improvements, including peripheral oxygen saturation, requiring ICU admissions, duration of hospitalization, chest CT involvements, WBC, and ESR. We suggest further studies on ARB using larger sample size and multicenter design.

Trial registration: IRCT20180725040596N2 on 18 April 2020.

Background

Coronavirus disease (COVID-19) is an infectious disease caused by a new coronavirus named SARS-COV-2. Majority of people infected by this virus will experience mild to moderate symptoms of respiratory illness. This virus transmit by droplets when an infected person sneezes or coughs (1).

Since COVID-19 was reported in December 2019 from Wuhan in China, more than 24 million cases of this disease have been reported from the world causing about 800,000 deaths (2). About 206 countries

are fighting with virus and the problem is going to be worse due to there are no specific vaccines or treatments for COVID-19. World Health Organization declared the outbreak of novel Corona virus a Public Health Emergency of International Concern, or PHEIC on January 2020 (3).

This is a severe problem for public health because the majority of infected persons has not symptoms and could transmit the disease to the others during the incubation period too (4).

There are currently no known effective therapy for infection with SARS-COV-2. For mild form of this disease is not a serious problem. But for moderate and severe forms of disease treatment is necessary. The treatment of patients with COVID-19 included supportive care to relief the symptoms mainly. Although WHO mentioned there is not any effective treatments for COVID-19 but there is some reporting about the use of some antiviral drugs (oseltamivir, lopinavir/ritonavir), antibiotics, Hydroxychloroquine and glucocorticoids for the treatment of this patients (4). However, there are many ongoing clinical trials evaluating potential treatments for COVID-19.

The other drugs also were recommended as a possible therapeutic options for the COVOD-19 such as Remdesivir and Chloroquine phosphate (5, 6).

Recently Australian scientists have published a research indicating that Ivermectin, an approved anti-parasitic drug is highly effective against the Covid-19 virus when applied to an infected cell culture (7).

Arbidol (ARB) is a Russian-made drug using for some enveloped and non-enveloped viruses. ARB is well known in Russia and China, and with a lesser extent in other countries but not in North America. Arbidol is using as a therapy for influenza A and B viruses, and recently for hepatitis C virus (HCV) (8, 9).

At present, there is not any potent and specific antiviral therapy or vaccine for SARS-COV-2. Therefore developing an effective drug for therapy or control of this disease is very critical option to control the COVID-19 outbreak.

The aim of current study is to determine the effect of ABD in treatment of COVID-19 disease.

Methods

Design and Participants

This open label randomized controlled trial of effectiveness of ARB on COVID-19 disease was conducted between 20 April and 18 June 2020 in a teaching hospital of Iran University of medical Sciences (IUMS), Tehran, Iran. The current clinical trial was done in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization–Good Clinical Practice guidelines. The study protocol was approved by ethics committee of IUMS (IR.IUMS.RCT.1399.090) and registered in Iranian Registry of Clinical Trials (IRCT) with register number of IRCT20180725040596N2 on 18 April 2020 (URL: <https://www.irct.ir/user/profile>). The study protocol and reporting of results were adhered to Consolidated Standards for Reporting Trials (CONSORT).

Eligible patients were non pregnant women and men aged 18 years old or more with definite diagnosis of COVID-19 by Real Time RNA specific Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) or computed tomography (CT) scan imaging (pneumonia), and oxygen saturation of 94% or less. The findings of CT were described as bilateral lung opacities and lobular and sub segmental areas of consolidation (10). The method of sampling was convenience from hospitalized patients who admitted to infectious ward of Firoozgar teaching hospital. We considered a significant level of 0.05 and 80% power to detect a moderate difference (Standardized difference =0.5) of hospitalization duration across two groups. Based on these criteria, the sample size was calculated as 50 per group (11).

Patients gave written informed consent according to regulations of ethics committee. Exclusion criteria included as: those who have a history of allergy to ARB class of drugs, abnormal liver or renal function, abnormal blood coagulation, ARB was used before inclusion, women who are nursing or pregnant and patients with severe heart disease.

Intervention

Participants were assigned to the intervention or control groups using blocked randomization method. Envelopes were prepared for unmasking. The random allocation procedure was performed by an independent staff of the hospital of RCT setting. The project manager and other colleagues of our study enrolled and assigned participants to interventions.

In this trial patients with diagnosis of Covid-19 received either Hydroxychloroquine (400 mg just on first day) followed by 400 mg Kaletra (Lopinavir-ritonavir) BD or Hydroxychloroquine (400 mg BD on first day followed by 200 mg BD) followed by ARB (200 mg TDS) 7 to 14 days based on the severity of disease. The 100 mg capsule of ARB was used in this trial.

Patients monitored daily for adverse events, vital signs and change of signs and symptoms. The current trial was monitored by research branch of Food and Drug administration organization of Iran.

Outcome measures

The primary outcome was hospitalization duration and clinical improvement 7 days after admission. The criteria of improvement were relief of cough, dyspnea and fever. Time to relieving fever was assessed across two groups too.

The secondary outcomes were death during 30 days of treatment, duration of hospitalization, changing laboratory tests during 7 days, changing of CT findings after 30 days and need to invasive mechanical ventilation.

We measures the age, gender, job, education status, underlying disease (history of diabetes, Ischemic heart disease, Hypertension, Asthma,..) and smoking status, as demographic variables. The fever, cough, dyspnea, nausea and vomiting, diarrhea, fatigue and weakness, and loss of appetite and taste were measured at the first day of admission. The saturation of peripheral oxygen, C-reactive protein (CRP),

Complete Blood Cell Count (CBC), Erythrocyte Sedimentation Rate (ESR), Aspartate transaminase (AST), Alanine aminotransferase (ALT), White Blood Cell Count (WBC), Lymphocyte and Neutrophil count, Neutrophil Lymphocyte ratio, Total Bilirubin, Blood Na and K, Creatinine and Thyroid Stimulating Hormone (TSH) were measured at the first day of admission and 7 days after. The CT scan and chest X-ray were taken at the first day of admission and 30 days after. The PCR test was taken at admission and the time of discharge.

We categorized the patients to three groups based on severity of disease according to the CT scan and chest X-ray findings. Mild, moderate and severe categories were defined as involvement of base, less and more than 50% of the lung field respectively in CXR and CT scan.

Statistical analysis

Data analysis was carried out using SPSS version 24 software (SPSS Inc., IL, USA). The normality of data was evaluated using Kolmogorov–Smirnov test. Descriptive statistics including mean, frequency, and standard deviation (SD) were calculated for all numeric variables and expressed as mean \pm SD. Chi-square test was used to compare the qualitative variables across two groups. For normally distributed variables, independent sample and paired t-test were used across groups and before-after analysis respectively. We also used one way Analysis of Variance (ANOVA) to assess numeric variables across groups more than two category. Correlation analysis was used to evaluate the association between numeric variables. The *B* regression coefficients, with 95% confidence intervals (CI), were obtained using multiple linear regression analysis to assess the covariates associated with duration of hospitalization adjusted. All analyses were performed two-sided and significant level was considered at 0.05.

Results

Of 104 recruited patients with covid-19 admitted to the hospital between 20 April and 18 June 2020, four subjects were excluded due to contraindication of ARB use. The remaining one hundred patients who fulfilled inclusion criteria were assigned to the study and randomized to Hydroxychloroquine plus Kaletra or Hydroxychloroquine plus ARB. We did not have any lost to follow-up, therefore 50 patients per group were entered to final analysis (Fig 1).

Table 1 illustrates the demographic characteristics of the patients. The mean age of the patients was 56.6 (17.8) and 56.2 (14.8) in ARB and Kaletra groups respectively. Majority of patients were male across two groups (66% and 54%). The percent of smokers in ARB group was significantly more than Kaletra group ($P=0.01$). About 40% of subjects reported history of contact with a patient with covid-19 during 2 weeks before admission.

In Table 2, clinical characteristics of the patients was shown. According to the signs and symptoms, the patients in ARB group had weakness and headache more than the other group. (70% and 26% versus 52%

and 8% respectively). About 81% of patients in Kaletra arm needed admission to Intensive care Unit (ICU) versus 18.6 % of ARB group. The duration of hospitalization in ARB group was less than Kaletra arm significantly (7.2 versus 9.6 days; $P=0.02$). The severity of disease based on CT scan and chest X-ray findings were different after 30 days of admission significantly despite of almost similar severity at the day of admission. The mild finding based on CT scan was about 81% versus 53.2% in ARB and Kaletra groups respectively. This result based on chest X-ray was 96% versus 67% in ARB and Kaletra arms respectively.

Time to relief fever was almost similar across two groups (2.7 versus 3.1 days in ARB and Kaletra arms respectively). Although the time for ARB group was less than Kaletra, but the difference was not statistically significant. The side effects of both drugs were not considerable. The most common adverse event was nausea and vomiting specially in Kaletra group. The intubation and need to mechanical ventilation rates were not different across two groups. Out of 100 patients, there was three deaths totally. One death was occurred in ARB and two deaths in Kaletra group (Table 2).

According to compare the laboratory findings across two groups, the conversion of CRP test was almost similar after 7 days of admission. Although, the two plus CRP was more between patients in Kaletra than ARB group (35% versus 20%) without statistically significant difference (Table 3).

The PCR of 50% of patients at the time of admission was positive. This proportion at the time of discharge from hospital was about 38% totally. The positive PCR rate at the time of discharge in Kaletra and ARB group was 23% and 14% respectively (Table 3).

Peripheral oxygen saturation rate was different after seven days of admission across two groups significantly (94% versus 92% in ARB and Kaletra groups respectively) ($P=0.02$). Also WBC and neutrophil counts, ESR and blood K were different significantly after seven days of admission between ARB and Kaletra arms despite of similar values at the time of admission. Totally apart from comparative groups, peripheral oxygen saturation, ESR, WBC, neutrophil and lymphocyte counts, neutrophil to lymphocyte ratio, and blood Na were different at the time of admission and seven days after significantly ($P < 0.001$) (Table 3).

Patients who had history of Ischemic heart disease (IHD) were hospitalized more than the patients without this history (11.3 (4.9) versus 8.1 (5.0) days). This difference was statistically significant at less than 0.1 $P= 0.09$ partially. The duration of hospitalization for patients with diabetes was also more than patients without this disease (10 (4.0) versus 7.8 (5.3) days). This difference was statistically significant ($P=0.04$). Based on CT scan findings at the time of admission, the patients who categorized in severe group hospitalized more days than the mild group. (12 (5.4) versus 2 (2.0) days) ($P<0.01$). Patients with more peripheral saturation of oxygen had a shorter duration of hospitalization than the patients with lower saturation significantly ($r = 0.50$; $P=0.01$). High WBC count at the time of admission was correlated with higher duration of hospitalization ($r = 0.27$; $P= 0.007$). The Na level and lymphocytosis at the time of admission were correlated with duration of hospitalization reversely ($r = -0.32$; $P=0.01$, $r = -0.15$; $P=0.05$ respectively) (data was not shown).

Based on multiple linear regression analysis, IHD, Na level and oxygen saturation at the time of admission and type of therapy were the independent adjusted variables that determined the duration of hospitalization in patients with covid-19. Also the lymphocytosis at the level of 0.06 probability value could be another determinant factor for duration of hospitalization (Table 4).

Discussion

Since COVID-19 has been pandemic, a variety of antiviral drugs have been investigated on patients with COVID-19 (12). Arbidol is a Russian antiviral drug that seems to be effective against many viruses including influenza A, B, and C, respiratory syncytial virus (RSV), severe acute respiratory syndrome-related coronavirus (SARS-CoV), adenovirus, parainfluenza, poliovirus, rhinovirus, coxsackievirus, zika virus, hepatitis B and C viruses (13-15). It has been demonstrated that Arbidol has a dual effect on cell attachment and replication, and thus a broad-spectrum effect on viruses (16, 8), so it is administered for post-exposure prophylaxis and treatment (17). Therefore, Arbidol is considered to be one of the antiviral drugs that can be effective in the treatment of COVID-19 patients.

In the present randomized controlled trial, we compared the antiviral effects and safety of Arbidol to Kaletra in COVID-19 patients and revealed several benefits in the Arbidol group. During the study, 100 patients were enrolled, 50 patients were assigned to receive Arbidol and 50 to receive Kaletra. We observed no differences in time to relief fever (2.7 vs. 3.1 days), intubation and ventilation (6% vs. 4%), conversion of CRP after seven days between Arbidol and Kaletra groups, respectively. Furthermore, compared to Kaletra, we found that Arbidol was significantly associated with higher peripheral oxygen saturation and lower amounts of WBC and ESR after seven days of admission.

We demonstrated that both drugs had no severe side effects. Similarly, some reports found no life-threatening adverse events in Arbidol and Kaletra groups (18, 19), except Li et al. study which presented an old male patient with a history of diabetes and hypertension in the Kaletra group, who experienced severe diarrhea on day 3 of initiating treatment (8). Although all of the patients in both groups had similar severity on admission, 18.6% of patients in Arbidol group were candidates for referring to the intensive care unit (ICU) during admission versus 81% of patients in Kaletra group. Patients in the Arbidol group spent a shorter duration of hospitalization (7.2 days) compared to Kaletra group (9.6 days, p-value= 0.02). Furthermore, 81% of patients in Arbidol group had mild involvement on the chest CT scan after 30 days of admission compared to 53% in Kaletra group (p-value= 0.004). Noteworthy, we noticed several demographic, clinical, and laboratory determinants of duration of hospitalization in COVID-19 patients, including IHD, oxygen saturation on admission, treatment with Arbidol, plasma Na levels, and lymphocytosis with a probability value of 0.06. In this regard, two cohort studies from Wuhan, China noted that COVID-19 patients aged ≥ 80 years and with lymphopenia ($<1.1 \times 10^9/L$) had a longer duration of hospitalization (20, 21).

Collectively, our findings indicate a lower proportion of ICU admissions, a shorter length of hospital stay, and a higher percentage of mild chest CT involvement after 30 days of admission among the COVID-19

patients who were treated with Arbidol compared to Kaletra, representing that Arbidol may be superior to Kaletra in the management of COVID-19 patients. Although, to date, no vaccines or antiviral drugs are approved for the treatment of COVID-19, "National Health Commission and National Administration of Traditional Chinese Medicine" have recently recommended Kaletra combined with Arbidol and reported its antiviral effects (22). However, to our knowledge, limited documents are evaluating the efficacy and safety of Arbidol on COVID-19 patients. Consistent with our study, a retrospective study from China compared the efficacy and safety of Kaletra to Arbidol in COVID-19 patients (19). They detected no viral load in the Arbidol group, while a viral load of 44.1% was found in the Kaletra group, concluded that Arbidol monotherapy might be more effective than Kaletra for COVID-19 treatment.

Similarly, another retrospective study found that Arbidol, combined with Kaletra, compared to Kaletra alone, would improve the viral clearance and chest CT scans (23). A cohort study of 504 hospitalized COVID-19 patients with mixed illness severities presented that Arbidol significantly reduced mortality (OR=0.183, 95% CI=0.075-0.446), and it was more likely to absorb lesions on chest CT scan (24). However, a randomized controlled trial by Li et al. and a retrospective study by Chen et al. suggested that neither the COVID-19 symptoms or chest CT involvement, nor the time to SARS-CoV-2 PCR negative in respiratory specimens was not improved/decreased in patients who received Kaletra and Arbidol (18, 25). Despite the small sample size in Li et al. study (8), they did not recruit severely or critically ill cases. Additionally, different from Li et al. (18), we gave Kaletra and Arbidol in combination with hydroxychloroquine to each group. Nevertheless, we believe that our findings are likely to help physicians develop appropriate treatment strategies among evolving evidence for COVID-19 management.

Limitations

The current study had some limitations. We could not measure the trend of changing clinical and laboratory variables daily. If this measure was done, we could compare trend of changing and improvement of symptoms and signs across two groups. The other limitation was access to the enough number of ARB drug. We had just some limited drugs to do the trial, so the larger sample size was not possible in order to assess the other important outcomes.

Conclusion

To the best of our knowledge, the present randomized controlled trial is the first study from Iran, highlighting the benefits of Arbidol monotherapy for the treatment of hospitalized COVID-19 patients. We have shown that Arbidol, compared to Kaletra, significantly contributes to clinical and laboratory improvements, including peripheral oxygen saturation, requiring ICU admissions, duration of hospitalization, chest CT involvements, WBC, and ESR. Based on eligibility criteria for enrollment of the patients in current study that were not very strict, the generalizability of our findings are acceptable.

Abbreviations

COVID-19: Corona Virus Disease 19, Arbidol: ARB, PHELC: Public Health Emergency of International Concern, SARS-Cov-2: Severe Acute Respiratory Syndrome Corona virus 2, WHO: World Health Organization, HCV: Hepatitis C Virus, IUMS: Iran University of Medical Sciences, CRP: C-reactive protein, CBC: Complete Blood Cell Count, ESR: Erythrocyte Sedimentation Rate, AST: Aspartate transaminase, ALT: Alanine aminotransferase, WBC: White Blood Cell Count, TSH: Thyroid Stimulating Hormone, IHD: Ischemic heart disease, RT-PCR: Reverse Transcriptase Polymerase Chain Reaction, CT: Computed Tomography, IRCT: Iranian Registry of Clinical Trials, CXR: Chest X ray, ANOVA: Analysis of Variance, TDS: Three times daily, BD: Twice daily, SPSS: Statistical Software for Social Sciences.

Declarations

Ethics approval and consent to participate

- The study protocol was approved by ethics committee of IUMS (IR.IUMS.RCT.1399.090). All patients signed informed consent to participate in the study.

Consent to publish

- Our manuscript does not contain data from any individual person (including individual details, images or videos).

Availability of data and materials

- The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing interests

- The authors declare that they have “no competing interests”.

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Authors' Contributions

- MN planned the methodology and was the major contributor in writing the manuscript; ZY contributed in writing the manuscript, HK assisted the implementation of the study; MJM, AL, MR, MeN, and ND gathered data and implemented the study and MR was the project manager of the study. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic Characteristics of the Patients by Treatment Groups.

Characteristics*	All patients (n=100)	Arbidol group (n=50)	Kaletra group (n=50)
Age, years (SD)**	56.4 (16.3)	56.6 (17.8)	56.2 (14.8)
Sex, n (%)	100 (100)	50 (100)	50 (100)
Male, n (%)	60 (60)	33 (66)	27 (54)
Female, n (%)	40 (40)	17 (34)	23 (46)
Marital status, n (%)	100 (100)	50 (100)	50 (100)
Single, n (%)	39 (39)	19 (38)	20 (40)
Married, n (%)	61 (61)	31 (62)	30 (60)
Job, n (%)	90 (100)	44 (100)	46 (100)
Hospital staff, n (%)	5 (5.5)	1 (2.3)	4 (8.7)
Self-employment, n (%)	32 (35.5)	16 (36.4)	16 (34.8)
Housekeeper, n (%)	35 (38.9)	15 (34.1)	20 (43.5)
Worker, n (%)	5 (5.6)	4 (9.1)	1 (2.2)
Employee, n (%)	13 (14.4)	8 (18.2)	5 (10.9)
Smoker, n (%)	15 (15)	12 (24)	3 (6)
Cigarette per day, n (SD)	12.2 (11.9)	13.5 (12.4)	5 (4.2)
Smoking duration, years (SD)	14.6 (8.2)	14.5 (8.6)	15 (7)
Comorbidities, n (%)	72 (72)	39 (78)	33 (66)
Hypertension, n (%)	39 (39)	22 (44)	17 (34)
Diabetes, n (%)	28 (28)	15 (30)	13 (26)
Coronary heart disease, n (%)	9 (9)	7 (14)	2 (4)
Asthma, n (%)	2 (2)	2 (4)	0 (0)
Chronic kidney disease, n (%)	2 (2)	1 (2)	1 (2)
Other diseases, n (%)	38 (38)	22 (44)	16 (32)

*Data is presented as mean (standard deviation), n (%) or n (SD); **Abbreviation: SD, standard deviation

Table 2. Clinical Characteristics of the Patients by Treatment Groups.

Characteristics	All patients (n=100)	Arbidol group (n=50)	Kaleta group (n=50)	<i>P</i> Value
Signs and Symptoms, n (%)				
Fever	46 (46)	19 (38)	27 (54)	0.1
Cough	80 (80)	41 (82)	39 (78)	0.6
Shortness of breath	66 (66)	33 (66)	33 (66)	0.99
Weakness	61 (61)	35 (70)	26 (52)	0.6
Anosmia	10 (10)	6 (12)	4 (8)	0.5
Diarrhea	15 (15)	12 (24)	3 (6)	0.01
Nausea and vomiting	26 (26)	11 (22)	15 (30)	0.3
Myalgia	45 (45)	20 (40)	25 (50)	0.3
Headache	17 (17)	13 (26)	4 (8)	0.01
Others	50 (50)	18 (36)	32 (64)	0.005
Hospitalization location, n (%)				
ICU, n (%)	88 (100)	43 (100)	45 (100)	0.09
Ward, n (%)	43 (48.8)	8 (18.6)	35 (81.4)	
	45 (51.1)	3 (6.7)	42 (93.3)	
Hospitalization duration, days (SD)	8.4 (5.1)	7.2 (4.7)	9.6 (5.2)	0.02
Time to stop fever, days (SD)	2.9 (1.3)	2.7 (1.1)	3.1 (1.4)	0.2
Illness severity, n (%)				
Mild	19 (19)	9 (18)	10 (20)	0.9
Moderate	58 (58)	29 (58)	29 (58)	
Severe	23 (23)	12 (24)	11 (22)	
CT scan in beginning, n (%)				
CT scan in beginning, n (%)	100 (100)	50 (100)	50 (100)	0.9
Involvement type, n (%)				
Mild	11 (11)	5 (10)	6 (12)	
Moderate	66 (66)	33 (66)	33 (66)	
severe	23 (23)	12 (24)	11 (22)	
CT scan in 30th day, n (%)				
CT scan in 30 th day, n (%)	97 (100)	49 (100)	48 (100)	0.004
Involvement type, n (%)				

Mild	63 (64.9)	38 (80.9)	25 (53.2)	
Moderate	31 (31.9)	9 (19.1)	22 (46.8)	
severe	0 (0)	0 (0)	0	
CXR in beginning, n (%)	100 (100)	50 (100)	50 (100)	0.3
Involvement type, n (%)				
Mild	25 (25)	11 (22)	14 (28)	
Moderate	66 (66)	36 (72)	30 (60)	
severe	9 (9)	3 (6)	6 (12)	
CXR in 30 th day, n (%)	97 (100)	49 (100)	48 (100)	<0.001
Involvement type, n (%)				
Mild	75 (77.3)	44 (95.7)	31 (67.4)	
Moderate	17 (17.5)	2 (4.3)	15 (32.6)	
severe	0 (0)	0 (0)	0 (0)	
Intubation, n (%)	5 (5)	3 (6)	2 (4)	0.6
Mechanical Ventilation, n (%)	5 (5)	3 (6)	2 (4)	0.6
Mortality, n (%)	3 (3)	1 (2)	2 (4)	0.5
Medication side effect, n (%)	15 (100)	3 (100)	12 (100)	0.1
Nausea/vomiting, n (%)	8 (53.5)	1 (33.3)	7 (58.3)	
Dizziness, n (%)	3 (20)	0 (0)	3 (25)	
Others, n (%)	4 (26.7)	2 (66.7)	2 (16.7)	

Note: Data are presented as mean (standard deviation) or n (%).

Abbreviation: ICU; Intensive Care Unit, CT; Computerized Tomography, CXR; Chest X-ray, SD; Standard Deviation..

Table 3. Laboratory findings of the Patients by Treatment groups

Laboratory findings	All patients (n=100)	Arbidol group (n=50)	Kaletra group (n=50)	<i>P</i> Value
CRP Base, n (%)	100 (100)	50 (100)	50 (100)	0.6
0, n (%)	16 (16)	7 (14)	9 (18)	
+, n (%)	29 (29)	15 (30)	14 (28)	
++, n (%)	29 (29)	17 (34)	12 (24)	
+++, n (%)	26 (26)	11 (22)	15 (30)	
CRP 7th day, n (%)	99 (100)	50 (100)	49 (100)	0.2
0, n (%)	33 (33.3)	17 (34)	16 (32.7)	
+, n (%)	38 (38.3)	23 (46)	15 (30.6)	
++, n (%)	27 (27.2)	10 (20)	17 (34.7)	
+++, n (%)	1 (2)	0 (0)	1 (2)	
PCR Base, n (%)	100 (100)	50 (50)	50 (50)	0.8
Positive, n (%)	51 (51)	25 (50)	26 (52)	
PCR Discharge, n (%)	97 (100)	49 (100)	48 (100)	0.2
Positive, n (%)	18 (38.2)	7 (14.3)	11 (22.9)	
Oxygen Saturation, % (SD)				<0.001
In admission	84.9 (8)	85.5 (8.4)	84.3 (7.7)	0.4
7 th day	93 (4.2)	93.9 (3.1)	92 (4.8)	0.02
Erythrocyte Sedimentation Rate, mm/h (SD)				<0.001
In admission				
7 th day	40 (19.9)	38.7 (19.7)	41.4 (20.3)	0.5
	27.8 (17.4)	23.3 (15.5)	32.2 (18.2)	0.01
White-cell count, ×10⁹/L (SD)				<0.001
In admission	10.1 (4.9)	10.5 (4.1)	9.8 (5.5)	0.4
7 th day	6.7 (2.2)	6.2 (1.7)	7.2 (2.5)	0.03
Lymphocyte count, ×10⁹/L (SD)				<0.001
In admission	20.4 (8.7)	20.3 (8.7)	20.4 (8.9)	0.9
7 th day	26.3 (10.6)	24.7 (8.9)	27.9 (12)	0.1

Neutrophil count, ×10⁹/L (SD)				<0.001
In admission	73.8 (11.2)	74.6 (9.7)	73 (12.6)	0.4
7 th day	65.9 (13.2)	69.1 (11.2)	62.7 (14.4)	0.01
Neutrophil/ Lymphocyte ratio (SD)				<0.001
In admission	4.7 (3.3)	4.8 (3.7)	4.6 (2.8)	0.7
7 th day	3.4 (3.7)	3.7 (4.3)	3.2 (2.9)	0.4
AST, IU/L (SD)				0.9
In admission	34.3 (19.9)	33.8 (23.7)	34.7 (15.5)	0.8
7 th day	32.5 (15.2)	31.1 (15.9)	33.8 (14.4)	0.3
ALT, IU/L (SD)				0.1
In admission	28.8 (16.4)	28.1 (18.2)	29.5 (14.6)	0.6
7 th day	30.2 (15.1)	28.3 (15.6)	32.2 (14.5)	0.2
Total Bilirubin, mg/dL (SD)				0.3
In admission	0.9 (0.5)	1 (0.5)	0.9 (0.4)	0.3
7 th day	1 (0.4)	1 (0.5)	1 (0.4)	0.8
Serum Creatinine, μmol/L (SD)				0.01
In admission	1 (0.6)	1.1 (0.8)	0.9 (0.2)	0.1
7 th day	0.9 (0.4)	1 (0.6)	0.9 (0.2)	0.1
Blood Sodium, mEq/L (SD)				<0.001
In admission	136.3 (3.7)	136.1 (3.8)	136.4 (3.6)	0.7
7 th day	140.5 (3)	140.7 (2.9)	140.3 (3.1)	0.5
Blood Potassium, mmol/L (SD)				0.08
In admission	3.9 (0.5)	3.9 (0.5)	3.9 (0.5)	0.9
7 th day	4 (0.5)	3.9 (0.4)	4.2 (0.5)	0.001
TSH, milli-international U/L (SD)				0.3
In admission	4.2 (1.8)	4.4 (1.9)	4.1 (1.7)	0.3
7 th day	4.1 (1.8)	4.2 (1.9)	4 (1.7)	0.5
Creatinine				0.007

In admission	1.05 (0.66)	1.14 (0.89)	0.96 (0.27)	0.17
7 th day	0.97 (0.48)	1.04 (0.64)	0.90 (0.20)	0.14

Note: Data are presented as mean (standard deviation) or n (%).

Abbreviation: CRP; C-Reactive Protein, PCR; Polymerase Chain Reaction, SD; Standard Deviation, U/L; Units/Liter, mm/h; Millimeter/Hour, SGOT; Serum Glutamic Oxaloacetic Transaminase, SGPT; Serum Glutamic-Pyruvic Transaminase, mg/dl; Milligrams per Deciliter, TSH; Thyroid Stimulating Hormone.

*P-values indicate differences between patients in the Arbidol and the Kaletra groups and between in hospital and 7th day laboratory findings. P < 0.05 was considered statistically significant.

Table 4. Regression analysis to determine factors associated with duration of hospitalization

Variables*			t	P Value	95.0% Confidence Interval for B	
	B	Std. Error			Lower Bound	Upper Bound
(Constant)	73.438	15.261	4.812	.000	43.129	103.747
Arbidol group	2.596	.837	3.102	.003	.934	4.258
Without IHD**	-3.842	1.482	-2.593	.011	-6.786	-.899
Without DM**	.122	1.005	.121	.904	-1.874	2.118
WBC	.113	.093	1.214	.228	-.072	.298
Oxygen saturation	-.238	.061	-3.900	.000	-.359	-.117
Lymphocytosis	-.089	.048	-1.865	.065	-.183	.006
Na level	-.300	.112	-2.670	.009	-.523	-.077

*The White blood cell count (WBC), lymphocytosis, Na level and Oxygen saturation are for the time of admission.

**Ischemic heart disease; Diabetes Mellitus

Figures

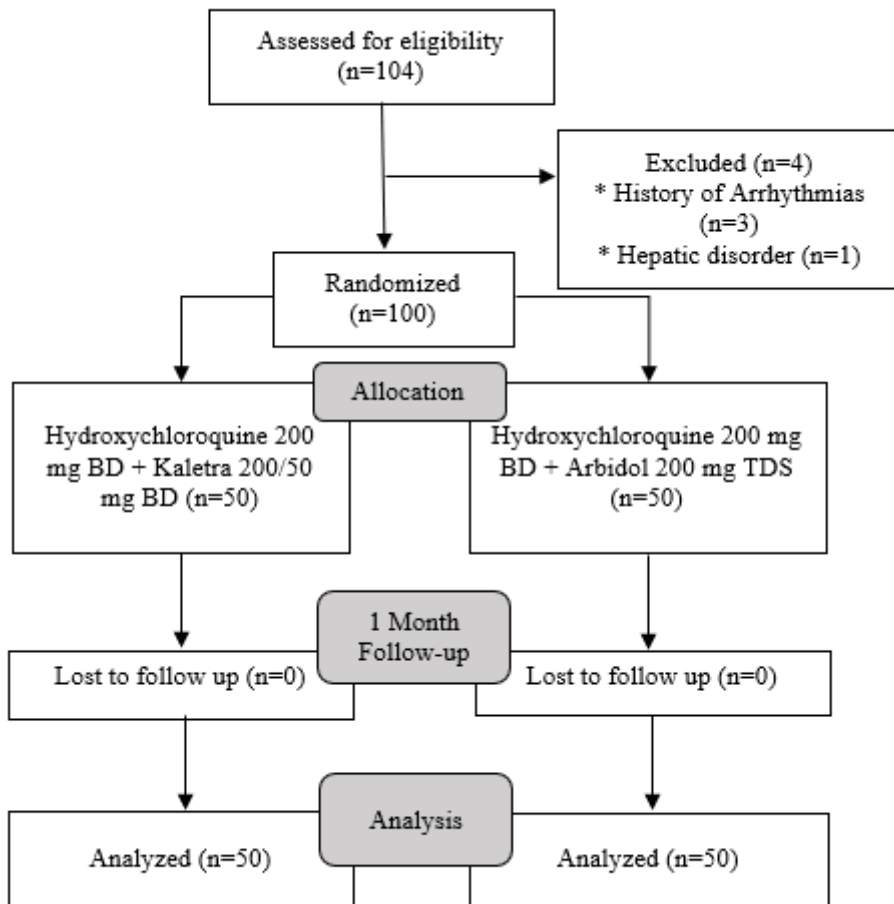


Figure 1

Consolidated standards of reporting trials (CONSORT) flow diagram.