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RESEARCH ARTICLE

The effect of lopinavir - ritonavir on mortality in COVID-19 pneumonia

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ABSTRACT

Aim: COVID-19 is a lethal disease for which there is still no specific treatment. The study aims to retrospectively investigate the effect of adding lopinavir/ritonavir to the treatment of patients using favipiravir (in the ward or intensive care unit) on mortality.

Methods: This study was conducted in 181 Rt-PCR(+) adult patients with severe and critical COVID-19. Demographic and laboratory data, antiviral agents used in treatment (with or without lopinavir-ritonavir), presence of intubation, and clinical outcome were recorded. The patients were categorized into Group 1 (not receiving lopinavir-ritonavir), Group 2 (administered lopinavir-ritonavir in ward), and Group 3 (administered lopinavir-ritonavir in the intensive care unit).

Results: The lowest mortality rate was found with Group 2 (21.4%) while this rate was 77.9% for Group 3 and 42.3% for Group 1 ($p<0.001$). There was no significant difference in length of hospital stay among groups ($p>0.05$). While 35.2% (25 patients) of Group 1 needed intubation, this rate was 21.4% (9 patients) in Group 2 ($p<0.001$).

Conclusions: This study demonstrated that lopinavir / ritonavir treatment reduced mortality and the need for intubation when initiated before the critical pneumonia phase. Lopinavir/ritonavir may be useful in the treatment of COVID-19, especially as part of the combination regimen.

Keywords: COVID-19, Lopinavir / ritonavir, pneumonia

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INTRODUCTION

The fatality rate of COVID-19 cases is 3.4% worldwide, which is higher than that of seasonal flu (1). There is no specific treatment for this lethal disease, and pharmacological agents are urgently needed. Lopinavir is an inhibitor of human immunodeficiency virus (HIV) type 1 aspartate protease and was approved for severe acute respiratory syndrome (SARS) infection in 2003. Ritonavir is combined with lopinavir to increase plasma half-life by inhibiting cytochrome P450 (2). In vitro studies have shown that lopinavir/ritonavir is effective against SARS-CoV-2 at acceptable concentrations (3).

In light of this information, this study was conducted to retrospectively examine the efficacy of adding lopinavir-ritonavir as an antiviral agent would prove in reducing mortality with the treatment of favipiravir continued for 10 days in the cases where pneumonia showed a progressive trend and inflammation markers continued to increase.

METHODS

Study design and participants

This study is a single-center, retrospective study, and it was conducted on patients hospitalized in the ward and intensive care unit at Izzet Baysal State Hospital (Bolu, Turkey). 181 Rt-PCR (+) adult patients with severe and critical COVID-19 pneumonia in line with WHO Interim guidance (3) were included as participants in the study.

Patients under 18 years of age, pregnant, and postpartum were not included in the study. The demographic and laboratory data of the patients, antiviral medications used, presence of intubation, and treatment results were recorded retrospectively. Favipiravir (2x1600 mg/day loading, 2x 600 mg/day maintenance) was given routinely to all patients, and lopinavir-ritonavir was added to some of the patients who developed severe or critical pneumonia despite using Favipiravir treatment. The patients were categorized as Group 1 (not receiving lopinavir-ritonavir), Group 2 (administered lopinavir-ritonavir in the ward), and Group 3 (administered lopinavir-ritonavir in the intensive care unit). Informed consent was obtained from the patients, and ethics committee approval was granted from the hospital (Date: 05.01.2021 / No: 2020/325).

Data collection

Laboratory data of the patients (complete blood count, biochemical parameters, coagulation parameters, procalcitonin) antiviral drug treatments (with and without lopinavir-ritonavir), length of hospital stay, and presence of intubation were recorded.

Outcomes

The primary outcome is mortality from hospital treatment. The secondary outcome is the length of stay in the hospital.

Statistical analysis

The data obtained in the study was analyzed in the SPSS 20 software. The normality of distribution was tested based on the coefficients of skewness and kurtosis with the ± 2 intervals in addition to the Kolmogorov-Smirnov test (4). One-way ANOVA test was used in comparing the arithmetic means of the groups with normal distribution. For the difference between groups, the Scheffe test was used if the variances were homogeneous; on the other hand, the Games-Howell test was used if the variances were not homogeneous. The Kruskal-Wallis test was used in comparing the medians of the groups that did not show normal distribution. Bonferroni correction was made to determine the difference when the difference between groups was significant. The relationship between categorical variables was examined by Chi-Square analysis. $p<0.05$ was determined as the level of statistical significance.

RESULTS

The mean age of the patients was 67.46 ± 14.09 years, and the mean age in Group 1 and Group 3 was significantly higher than that of Group 2 ($p<0.05$) (Table 1). Troponin values of Group 1 and 3 were found to be significantly higher than group 2 ($p<0.05$), but

no significant difference was found between Group 1 and 3 (p>0.05). Procalcitonin values of Group 3 were significantly higher than those in Group 2 (p<0.05). There was no significant difference between the other groups (p>0.05) (Table 2).

Table 1. Relationship of groups with gender, intubation and mortality

	Group 1 (n=71, 39.2%)	Group 2 (n=42, 23.2%)	Group 3 (n=68, 37.6%)	All patients (n=181)	x^2 value	p-value
Gender					2.496	0.287
Female	18 (25.4%)	16 (38.1%)	24 (35.3%)	58 (32.0%)		
Male	53 (74.6%)	26 (61.9%)	44 (64.7%)	123 (68.0%)		
Intubation					86.398	0.000*,1
Yes	25 (35.2%)	9 (21.4%)	68 (100%)	102 (56.4%)		
No	46 (64.8%)	33 (78.6%)	0 (0.0%)	79 (43.6%)		
Mortality					36.614	0.000*,1
Cured	41 (57.7%)	33 (78.6%)	15 (22.1%)	89 (49.2%)		
Exitus	30 (42.3%)	9 (21. %4)	53 (77.9%)	92 (50.8%)		

* p<0.05 statistically significant, [1] Chi-Square test

Table 2. Mean ± SD values of laboratory values

	Group 1 (n=71, 39.2%)	Group 2 (n=42, 23.2%)	Group 3 (n=68, 37.6%)	All patients (n=181)	p-value
$\bar{x}$ ± SS					
Age	68.62±12.22[a]	58.38±14.97[b]	71.85±12.97[c]	67.46±14.09	**0.000*,1 a>b (0.000) c>b (0.000)**
CRP (mg/L)	99.38±39.64	89.26±44.78	92.82±48.85	94.5±44.42	0.466
Ferritin (ug/L)	540.46±428.17	391.30±329.59	496.69±404.79	489.28±400.33	0.158
Median (Q1-Q3)					
Length of stay	12 (7-22)	9 (6-15)	9 (5-13.5)	10 (6-18)	0.060
D-Dimer (mg/L)	0.42 (0.21-1.13)	0.43 (0.16-0.75)	0.48 (0.27-1.13)	0.44 (0.22-1)	0.532
Troponin (ng/L)	13.7 (7.1-35.8)[a]	7.35 (4.9-15)[b]	19.5 (10-40.2)[c]	12.55 (6.6-30.08)	**0.000*,2 a>b (0.008) c>b (0.000)**
Lymphocyte (K/uL)	0.7 (0.4-1)	0.8 (0.5-1.4)	0.8 (0.5-1.15)	0.7 (0.5-1.1)	0.122
Lymphocyte % (K/uL)	9.9 (5.3-18.1)	10.7 (7-15.9)	9.8 (4.4-14.3)	10 (5.3-16.2)	0.193
LDH (U/L)	440 (332-610)	477 (384-585)	451 (321-586)	467.5 (335.5-591.25)	0.547
Procalcitonin (ng/mL)	0.14 (0.05-0.62)[a]	0.115 (0.045-0.32)[b]	0.31 (0.1-0.99)[c]	0.17 (0.06-0.68)	**0.007*,2 c>b (0.011)**
Thrombocyte (K/uL)	193 (139-262)	216 (173-285)	199.5 (144-255.5)	207 (149-263.5)	0.189

* p<0.05 Statistically significant, [1] One-Way ANOVA, [2] KWH:Krukal-Wallis H test

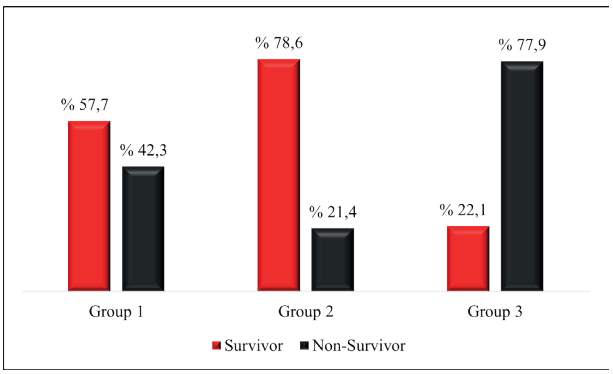

Figure 1. Mortality rates in treatment groups.

The mortality rate in Group 3 (53 patients, 77.9%) and Group 1 (30 patients, 42.3%) is significantly higher than in Group 2 (9 patients, 21.4%) (p <0.05) (Figure 1). While the need for intubation was 35.2% in group 1, this rate was found to be 21.4% in Group 2 during the clinical observation (p<0.05). Lopinavir/ritonavir was added to the treatment of Group 3 while the patients in this group were already intubated. There was no significant difference in length of hospital stay between groups (p>0.05).

DISCUSSION

In COVID-19, antivirals (lopinavir-ritonavir, remdesivir, interferons, chloroquine, and hydroxychloroquine), anti-inflammatory agents (glucocorticoids, tocilizumab), immunotherapy (convalescent plasma) and adjuvant treatments (herbal medicine, hormones, mesenchymal stem cells) are emphasized (5).

Favipiravir is a nucleotide analogue and RNA polymerase inhibitor, and it is included in the standard treatment in the COVID-19 Guide of the Ministry of Health in our country (6). While the patients included in the study were using favipiravir (2x1600 mg/day loading, 2x600 mg/day maintenance), they were hospitalized in the service or intensive care unit due to the progress of severe or critical COVID-19 pneumonia. While Favipiravir treatment of all patients was completed within 10 days, Lopinavir 200 mg/ritonavir 50 mg (2x400/100 mg, oral) was added to the treatment of one group of patients. The patients were categorized into Group 1 (not receiving lopinavir-ritonavir), Group 2 (administered lopinavir-ritonavir in the ward), and Group 3 (administered lopinavir-ritonavir in the intensive care unit).

The mean age of the patients was 67.46 ± 14.09 years, and the mean age in group 1 and group 3 was significantly higher than in group 2 (p<0.05). The Centers for Disease Control (CDC) indicate that age is a risk factor for severe diseases and complications (7).

Troponin values of Group 1 and 3 were found to be significantly higher than group 2 (p<0.05), but no significant difference was found between Group 1 and 3 (p>0.05). Guo et al. (8) found troponin increase in 27.3% of the patients hospitalized with the diagnosis of COVID-19 and reported increased hospital mortality in those patients as compared to the patients with normal troponin values. (59.6 % and % 8,9, p<0.001).

Procalcitonin values were significantly higher in Group 3 than in Group 2 (p<0.05). There was no significant difference between the among groups (p>0.05). In the meta-analysis study by Lippi et al. (9), it was reported that the risk of serious SARS-CoV-2 infection increased approximately 5-fold with increasing procalcitonin values. Procalcitonin levels could be an indicator of the severe course of COVID-19 (10).

The mortality rate in Group 3 (53 patients, 77.9%) and Group 1 (30 patients, 42.3%) was significantly higher than Group 2 (9 patients, 21.4%) (p<0.05). There was no significant difference between the three groups in terms of length of hospital stay (p>0.05). This result shows that adding lopinavir/ritonavir to the treatment does not increase the cost of hospitalization. While 35.2% (25 patients) of the participants in Group 1 needed intubation, this rate was 21.4% (9 patients) in Group 2 during clinical observation (p<0.05). Lopinavir/ritonavir was added to the treatment of the patients in group 3 while they were already under intubation. Mortality after intubation is generally quite high in COVID-19. One cohort study reported 32 mortalities out of 33 intubated patients (97%) (11), while another cohort study reported 30 mortalities out of 37 patients (81%) (12).

In a randomized controlled study, no significant relationship was found between lopinavir-ritonavir treatment and mortality or clinical improvement in COVID-19 as compared to standard support therapy. However, in the group receiving lopinavir-ritonavir, the need for non-invasive or invasive mechanical ventilation for serious complications (including acute kidney injury and secondary infections) and respiratory failure was reported to be less than in the group receiving no treatment (13).

Some studies also report that lopinavir–ritonavir treatment does not have any positive effects (13) and that this treatment does not cure clinical outcomes in patients hospitalized with the diagnosis of COVID-19 (14).

In the study comparing favipiravir and lopinavir/ritonavir treatment, viral clearance time was shorter and radiological improvement was higher in the favipiravir group (15). However, there are no studies on favipiravir and lopinavir/ritonavir combination. It has been reported to be beneficial in only 3 disease case series (16). However, combinations with other agents have been studied. For example, when lopinavir/ritonavir, hydroxychloroquine and interferon-b-1b were given to 5 severe cases of COVID-19 pneumonia, all patients recovered, and no significant side effects were observed (17).

CONCLUSIONS

These clinical studies are generally conducted on small numbers of cases and are not placebo-controlled, therefore additional studies are needed. The study showed that when lopinavir/ritonavir treatment is initiated in the ward prior to the onset of critical pneumonia stage, it reduces mortality and the need for intubation. In conclusion, lopinavir / ritonavir may be useful in the treatment of COVID-19, especially as part of the combination regimen.

Ethical approval

This study has been approved by the Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee (approval date 05.01.2021, number 2020/325). Written informed consent was obtained from the participants.

Author contribution

Concept: MED, EA, MB; Design: MED, EA, MB; Data Collection or Processing: MED, EA, MB; Analysis or Interpretation: MED, EA, MB; Literature Search: MED, EA; Writing: MED, EA, MB. All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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