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Clinical Outcomes of COVID-19 Patients Following Treatment with Atorvastatin: A Non-Randomized Clinical Trial

Resultados clínicos de pacientes con COVID-19 después del tratamiento con atorvastatina: un ensayo clínico no aleatorizado

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Abstract

Objective: There are controversial data regarding the utility of statins in hospitalized COVID-19 patients. This study aimed to assess the efficacy of statins on clinical outcomes of patients hospitalized with COVID-19.

Methods: A non-randomized clinical trial was performed among confirmed COVID-19 patients who were admitted to the BooAli hospital in Tehran, Iran. The intervention group received atorvastatin 20 mg orally once daily plus standard of care, while the control group received standard of care alone. The primary endpoints were clinical improvement rate at day 7 as well as in-hospital mortality rate. The secondary endpoints were the duration of hospitalization, the number of intensive care unit (ICU) admissions, the number of patients who needed invasive mechanical ventilation, the incidence of acute respiratory distress syndrome (ARDS), and the reduction of inflammatory markers.

Result: In total 94 patients were enrolled (treatment group: 41 patients, control group: 53 patients). The results showed that nearly 59% of patients who received atorvastatin manifested clinical improvement within 7 days compared to 62% of patients in the control group (P > 0.05). There was no significant difference between treatment and control groups in terms of in-hospital mortality, duration of hospitalization, ICU admissions, need for invasive mechanical ventilation, and incidence of ARDS.

Conclusion: Atorvastatin 20 mg daily in hospitalized COVID-19 patients was not associated with significant changes in clinical improvement of patients within 7 days, in-hospital mortality rate, and other clinical outcomes.

Keywords: COVID-19, SARS-CoV-2, Statin, Atorvastatin.

Resumen

Objetivo: Existen datos controvertidos sobre la utilidad de las estatinas en los pacientes hospitalizados por COVID-19. Este estudio tiene como objetivo evaluar la eficacia de las estatinas en los resultados clínicos de los pacientes hospitalizados con COVID-19.

Métodos: Se realizó un ensayo clínico no aleatorizado entre pacientes con COVID-19 confirmados que fueron ingresados en el hospital BooAli de Teherán, Irán. El grupo de intervención recibió atorvastatina 20 mg por vía oral una vez al día más el tratamiento estándar, mientras que el grupo de control recibió únicamente el tratamiento estándar. Los criterios de valoración primarios fueron la tasa de mejora clínica en el día 7 y la tasa de mortalidad hospitalaria. Los criterios de valoración secundarios fueron la duración de la hospitalización, el número de ingresos en la unidad de cuidados intensivos (UCI), el número de pacientes que necesitaron ventilación mecánica invasiva, la incidencia del síndrome de dificultad respiratoria aguda (SDRA) y la reducción de los marcadores inflamatorios.

Resultado: En total se inscribieron 94 pacientes (grupo de tratamiento: 41 pacientes, grupo de control: 53 pacientes). Los resultados mostraron que casi el 59% de los pacientes que recibieron atorvastatina manifestaron una mejora clínica en un plazo de 7 días, en comparación con el 62% de los pacientes del grupo de control (P > 0,05). No hubo diferencias significativas entre los grupos de tratamiento y de control en cuanto a la mortalidad intrahospitalaria, la duración de la hospitalización, los ingresos en la UCI, la necesidad de ventilación mecánica invasiva y la incidencia de SDRA.

Conclusiones: La administración de 20 mg diarios de atorvastatina en pacientes hospitalizados por COVID-19 no se asoció a cambios significativos en la mejoría clínica de los pacientes en un plazo de 7 días, la tasa de mortalidad intrahospitalaria y otros resultados clínicos.

Palabras clave: COVID-19, SARS-CoV-2, Estatina, Atorvastatina.

Introduction

The coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected the lives of millions of people globally since its recognition in December 2019. The clinical spectrum of SARS-CoV-2 infection ranges from mild to critical. According to one of the earliest studies by the Chinese Center for Disease Control and Prevention, 81% of the patients exhibited mild illness, and about 14% had severe symptoms (dyspnea, hypoxia, or more than 50 percent lung involvement on imaging within 24 to 48 hours), and about 5% were critically ill (respiratory failure, shock or multiorgan dysfunction)[1,2]. In critically ill patients, viral pneumonia can progress to acute respiratory distress syndrome (ARDS)[1,2]. The in-hospital mortality rate among COVID-19 patients was reported to be between 9.3% and 19.7% in a study in 2020[3]. Among patients with COVID-19, there is a high prevalence of cardiovascular disease with a considerably higher mortality rate4. Because antiviral agents and vaccines are not easily available in some countries or not sufficiently effective against different SARS-CoV-2 variants[5], repurposing existing medicines with various mechanisms, that are widely available, safe, and inexpensive is of great importance for identifying effective therapies against COVID-19.

Statins are conventionally used as the first-line treatment of dyslipidemia. The clinical benefits of statins for patients with cardiovascular disease are firmly established, they are vastly used in patients with or at risk of cardiovascular disease to decrease the rate of myocardial infarction, stroke, and cardiovascular death[6]. Statins have antithrombotic and antifibrotic as well as anti-inflammatory effects[7-10]. In a previous study, statin use was associated with a decrease in inflammatory markers such as C-reactive Protein (CRP)[11]. An increase in several biomarkers including the level of CRP has been shown to be associated with an increased risk of mortality in COVID-19 patients[12-14]. Interestingly, in seasonal influenza outbreaks, statin use was associated with reduced mortality in patients hospitalized with influenza virus infection[15,16]. Thus, adding statins as adjuvant therapy seems to be beneficial for COVID-19 patients. To date, several studies have investigated the use of statins in the treatment of COVID-19[17-21]. However, the results have been discordant. Therefore, this prospective study was designed to evaluate the efficacy of statins on clinical outcomes of patients hospitalized with COVID-19.

Methods

Study Design and Sample Size
This prospective non-randomized study was conducted between April and May 2020 at the BooAli Hospital in Tehran, Iran. The sample size of the study was calculated based on our previous data which showed about 50% of patients admitted to the hospital found the criteria for clinical improvement on day 7. We set an α-error of 0.05 and a power of 0.8 and the sample size calculated was 38 patients for each group to show a 30% difference in recovery. This study was approved by the Ethics Committee and the Research Council of Islamic Azad University, Tehran Medical Branch (ID: IR.IAU. PS.REC.1399.002) and was approved by the Iranian Registry of Clinical Trials (ID: IRCT20200413047062N1).

Eligibility Criteria and Intervention
Eligible patients were men and non-pregnant women with COVID-19 who were aged at least 18 years with positive reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 or confirmed computed tomography (CT) scan findings. Exclusion criteria included pregnancy or breastfeeding; hepatic cirrhosis; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than five times the upper limit of normal; known severe renal impairment; estimated glomerular filtration rate (eGFR) <30 mL/min, history of allergy to atorvastatin and history of severe adverse effect with statins.

The study intervention was atorvastatin 20 mg orally once daily until discharge from the hospital. Patients in both treatment and control groups received hydroxychloroquine 200mg twice daily for 5 to 7 days or lopinavir/ritonavir 400/100 mg tablets twice daily for 5 to 7 days as the treatment protocol of the hospital.

Laboratory tests for hematological and renal functions were evaluated by white blood cells, hemoglobin, platelet counts, eGFR, and blood urea nitrogen (BUN); liver function was assessed with AST, ALT, alkaline phosphatase (ALP). The serum level of CRP was evaluated as a marker of inflammation.

Outcomes
The primary endpoint of the study was clinical improvement within 7 days from the first day of hospitalization. Clinical improvement was defined as the time from the first day of hospitalization to an improvement of two points on a seven-category ordinal scale or live discharge from the hospital, whichever came first[22]. The seven-category ordinal scale consisted of the following categories: 1, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 6, hospitalized, requiring invasive mechanical ventilation; and 7, death. Another primary endpoint was the in-hospital mortality rate of the patients in the treatment and control groups. The secondary outcomes evaluated were the duration of hospitalization, the number of patients who needed invasive mechanical ventilation, the number

of ICU admissions, the incidence of ARDS, and the comparison of baseline CRP and CRP level at the end of treatment between atorvastatin and control groups.

Statistical Analysis

The results were analyzed using IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA). Quantitative variables were presented as mean and standard deviation and an Independent-Samples T-Test was used for group comparison. Categorical variables were presented as numbers and percentages. The Chi-square test was used for the comparison between the two groups. Paired-Samples T-Test was used for the comparison of baseline CRP level with CRP level at the end of treatment in the atorvastatin and control groups. Time to death was evaluated using survival analysis. The Kaplan-Meier method was used to estimate the time to death between the treatment and control groups, and the survival functions between the groups were compared using the Log-Rank (Mantel-Cox) test. $P < 0.05$ was considered statistically significant.

Results

General characteristics of the enrolled patients

Figure 1 shows the flow chart of all the patients evaluated and included in the study. Of 111 patients assessed for eligibility, 109 patients were enrolled in this study: 48 assigned to the atorvastatin group and 66 assigned to the control group. After the exclusion of 14 patients, 41 patients in the atorvastatin group and 53 patients in the control group were included in the analysis of the study.

**Figure 1:** Flow chart of patients enrolled in the study.
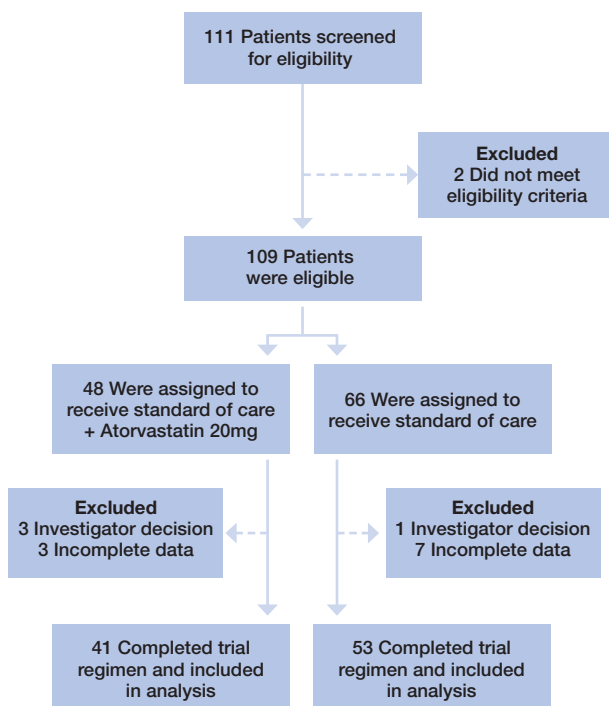
Analysis of baseline characteristics of both groups is summarized in **table I**. Overall, the mean age of study participants was 60 years and 42 (50.5%) were male. The mean BMI in the atorvastatin group and control group was 26.7 and 26.5 kg/m^2, respectively. The mean body temperature was 37.9°C in the atorvastatin group and 37.8°C in the control group and the mean respiratory rate at the time of enrolment was 19.5 and 18.6 breaths/min in the atorvastatin and control groups, respectively. The mean duration of symptoms before hospital admission was 5 days in both groups. In the atorvastatin group, 43.9% of the patients were previously diagnosed with hypertension while in the control group it was 32.0%. All the patients received hydroxychloroquine and 43.9% in the atorvastatin group and 41.5% in the control group received lopinavir-ritonavir as an antiviral medication. The data demonstrated that the demographic, clinical, and laboratory characteristics of the two groups were not significantly different.

Primary and secondary outcomes

The endpoint powered in this study was the clinical improvement rate at day 7 based on the seven-category ordinal scale. As shown in **table II** in the atorvastatin group, 24 (58.5%) patients were clinically improved by day 7, while in the control group 33 (62.3%) patients were improved. The difference was not statistically significant. The other primary endpoint was the assessment of the in-hospital mortality rate. The percentage of participants who died was 9.8% among those who received atorvastatin and 13.2% among the patients who did not. However, the difference in mortality rate between the two groups was not statistically significant. **Figure 2** shows the Kaplan-Meier survival curve of the two groups, and the log-rank test demonstrates no significant difference between atorvastatin and control groups.

The secondary endpoint of the study was the comparison of the duration of hospitalization between the two groups. In patients who received atorvastatin, the mean duration of hospitalization was not significantly different from the

Figure 2: Kaplan-Meier curves estimated the mortality of patients in the 2 groups of treatment and control. Log-rank test: P = 0.26.
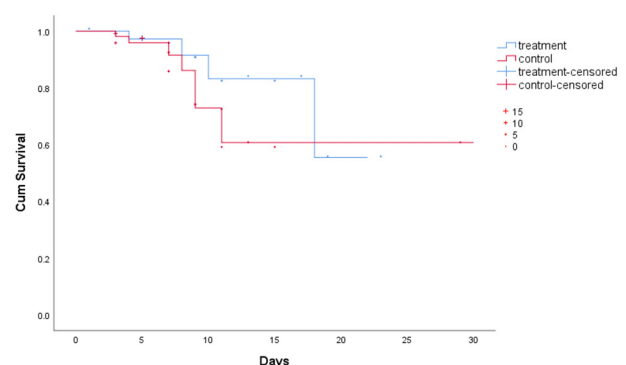
control group (7.9 ± 5.0 days vs 6.8 ± 4.4 days). Also, the mean duration of hospitalization was assessed for survived patients (excluding deaths) which were 7.7 ± 5.0 days and 6.7 ± 4.6 days in the atorvastatin and control groups respectively with no significant difference (**Table II**).

Other secondary endpoints were to compare the number of patients who needed ICU admission during hospitalization, the number of patients who needed invasive mechanical ventilation, and the incidence of ARDS between the two groups. **Table II** shows the percentage of ICU admissions in patients who received atorvastatin compared to those in the control group (19.5% vs 24.5%). The percentage of invasive mechanical ventilated patients was 14.6% and 22.6% in the atorvastatin and control groups, respectively. In the atorvastatin group, 14.6% of patients experienced ARDS, whereas in the control group 26.4% of patients experienced it. The differences in all these secondary outcomes were not statistically meaningful.

Table I: Patient Characteristics and Baseline Values.

Characteristics	Atorvastatin N= (41)	Control N= (53)	P value
Male, N (%)	24 (58.5%)	24 (45.3%)	0.20
Age (year), Mean (SD)	62 (12)	60 (14)	0.36
BMI (kg/m²), Mean (SD)	26.7 (3.6)	26.5 (4.8)	0.81
Clinical features at the time of enrollment, Mean (SD)			
Body temperature (°C)	37.9 (0.6)	37.8 (1.0)	0.57
Respiratory rate (breaths/min)	19.5 (3.8)	18.6 (2.8)	0.15
Duration of symptoms before hospital admission (days)	5.0 (2.7)	5.0 (2.4)	0.77
Underlying medical condition, N (%)			
Hypertension	18 (43.9%)	17 (32.0%)	0.23
History of Immunocompromised condition	3 (7.3%)	3 (5.7%)	0.74
Concomitant medications, N (%)			
Hydroxychloroquine	41 (100%)	53 (100%)	
Lopinavir-ritonavir	18 (43.9%%)	22 (41.5%)	0.81
Laboratory values at baseline, Mean (SD)			
White blood cells count (×109/L)	7.8 (4.5)	6.9 (3.5)	0.29
Absolute neutrophil count (×109/L)	6 (4.4)	5.3 (3.0)	0.36
Hemoglobin level (g/dL)	12.6 (2.3)	12.1 (1.5)	0.26
Platelet count (×109/L)	215.1 (88.5)	240.7 (98.7)	0.19
Estimated glomerular filtration rate (mL/min)	84.4 (32.0)	81.1 (33)	0.62
Creatinine (mg/dL)	1.01 (0.4)	1.10 (0.6)	0.39
Blood urea nitrogen (mg/dL)	21.6 (12.7)	19.0 (10.7)	0.28
Aspartate transaminase (U/L)	29.5 (11.3)	31.4 (15.4)	0.51
Alanine transaminase (U/L)	28.1 (13.1)	32.3 (17.0)	0.19
Alkaline Phosphatase (U/L)	204.5 (82.5)	191.6 (134.1)	0.59
C-reactive protein (mg/L)	37.4 (20.8)	37.0 (16.7)	0.93

N: Number; SD: Standard deviation; BMI: Body mass index; Independent-Samples T-Test was used for continuous variables; Chi-Square test was used for the categorical variables; P < 0.05 was considered significant.

Table II: Clinical outcomes.

Outcomes	Atorvastatin N= (41)	Control N= (53)	P value
Clinical improvement rate at day 7, N. (%)	24 (58.5%)	33 (62.3%)	0.71
Mortality during hospitalization, N. (%)	4 (9.8%)	7 (13.2%)	0.60
Duration of hospitalization (days), Mean (SD)	7.9 (5.0)	6.8 (4.4)	0.26
Duration of hospitalization among patients who survived, Mean (SD)	7.7 (5.0)	6.7(4.6)	0.73
Admission to ICU during hospitalization, N. (%)	8 (19.5%)	13 (24.5%)	0.56
Invasive Mechanical ventilation during hospitalization, N. (%)	6 (14.6%)	12 (22.6%)	0.32
Incidence of ARDS, N. (%)	6 (14.6%)	14 (26.4%)	0.16

N: Number; SD: Standard deviation; ICU: Intensive care unit; ARDS: Acute respiratory distress syndrome; Independent-Samples T-Test was used for continuous variables; Chi-Square test was used for the categorical variables; P < 0.05 was considered significant.

Table III: The behavior of CRP during the two different treatments.

	Atorvastatin N = (41)			Control N = (53)		
	Baseline	End of treatment	P Value	Baseline	End of treatment	P value
CRP (mg/L), Mean (SD)	37.3 (20.8)	27.2 (18.1)	0.006	37 (16.7)	35.2 (19.9)	0.418

CRP: C-reactive protein; SD: Standard deviation; Paired-Samples T-Test was used for the comparison of baseline CRP level vs. CRP level at the end of treatment; P < 0.05 was considered significant.

The comparison of CRP level, which was assessed as an inflammatory marker, on the first day of hospitalization and the end of treatment between the 2 groups is shown in **table III**. A significant decrease in CRP level was observed at the end of treatment in patients receiving atorvastatin (P=0.006), while it was not seen in the control group.

Discussion

In this study of patients with COVID-19 admitted to the BooAli hospital in Tehran, Iran, the use of atorvastatin 20 mg once daily compared with the control group was not associated with a significant difference in the primary outcome, clinical improvement within 7 days from the first day of hospitalization which was defined as the time from the first day of hospitalization to an improvement of two points on a seven-category ordinal scale or live discharge from the hospital, whichever came first. To our knowledge, this is the first study evaluating the effect of statins on clinical improvement based on a seven-category ordinal scale in COVID-19 patients. Results of our study were not associated with diminutions in in-hospital mortality and duration of hospital stay. This is in agreement with the results of a systematic review and meta-analysis of 3449 COVID-19 patients that evaluated the association between statin use and in-hospital outcomes of COVID-19 infection, suggesting that statin use did not improve mortality from COVID-19 infection[23]. Also, a randomized clinical trial of COVID-19 patients reported that adding atorvastatin to the standard of care in this study increased hospitalization days and the frequency of ICU admission[24]. In addition, a retrospective study evaluated the effect of statins on patients with COVID-19. The findings of this study could not demonstrate a significant association between statin use and a reduction in mortality rate in patients with COVID-19[25]. The INSPIRATION-S, a multicenter, randomized controlled trial also failed to show that atorvastatin was beneficial in critically ill COVID-19 patients[21].

However, there are studies reporting that statin use was associated with improved clinical outcomes in COVID-19 patients[26]. A meta-analysis of retrospective observational studies showed that statin therapy was associated with a 35% decrease in the adjusted risk of mortality in hospitalized COVID-19 patients[27]. In another study, 40 patients were randomized into a treatment group receiving atorvastatin + lopinavir/ritonavir or a control group receiving lopinavir/ritonavir alone. The primary endpoint of this study was the duration of hospitalization. The results showed that the duration of hospitalization in the lopinavir/ritonavir + atorvastatin group was significantly reduced compared to the control group, but there was no significant difference in the invasive mechanical ventilation reception[28]. In our study, the percentage of patients admitted to the ICU and invasive mechanical ventilated patients was lower in the treatment group, but the difference was not statistically significant. In another

study that analyzed a retrospective cohort of patients admitted to a tertiary center in Singapore for COVID-19 infection in a nested case-control design, through logistic treatment models with 1:3 propensity matching for age, gender, and ethnicity, statin use was independently associated with lower ICU admission[29].

In the current study, due to anti-inflammatory effects reported for statins, the level of CRP, as a marker of inflammation, was measured at baseline and at the end of treatment in both groups to observe whether there was any difference in the behaviour of this marker between the two groups. The results showed a significant decrease in the amount of CRP at the end of treatment in patients who received atorvastatin, whereas no significant decrease was seen in the control group. Although the reduction of CRP level was significant for the treatment group, still it was not in the normal range at the end of treatment. This was in concordance with the result of another study investigating the effect of statins on the behaviour of CRP during hospitalization in COVID-19 patients[28]. One of the key features of COVID-19 is the overwhelming inflammation observed in some patients, especially those who develop severe illness; thus, it is important to determine the optimum method to reduce inflammation and statins could be a candidate[30]. However, some of the studies claimed that due to the lower anti-inflammatory effects of statins compared to corticosteroids, statins cannot make a significant change in the inflammation or occurrence of cytokine storm in COVID-19, thus statin administration is not associated with alterations in the in-hospital outcomes of COVID-19 patients[31,32]. Overall, the current trial could not support a large benefit from statin treatment in COVID-19 patients. Yet, the absence of clinical benefit of atorvastatin in this study might be due to the small sample size. Therefore, we suggest conducting further studies with larger sample size. A potential limitation of our study was that the patients were not randomized for the treatment assignment. The absence of long-term follow-up was another limitation of this study.

Conclusion

The results obtained in the present study showed that in patients with COVID-19 admitted to the BooAli Hospital in Tehran, Iran, treatment with atorvastatin 20 mg daily was not associated with a significant difference in clinical improvement rate at day 7, in-hospital mortality rate, length of hospitalization, ICU admissions, need for invasive mechanical ventilation or incidence of ARDS. The effect of atorvastatin was only significant in reducing CRP levels from the first day of hospitalization until the end of treatment. The effect of more potent doses of statins needs to be investigated using larger sample sizes in future studies.

Conflict of Interest
The authors declare no conflict of interest.

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