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The effect of interferon in the therapy of severe coronavirus infection

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Abstract:

BACKGROUND: So far, several protocols have been used for the treatment of coronavirus disease-2019 (COVID-19). In this study, we aimed to study the effect of interferon on the treatment of hypoxemia caused by COVID-19.

MATERIALS AND METHODS: This was a quasi-experiment with a nonequivalent group design. All participants were admitted to Shahid Beheshti Hospital, Qom province. In total, 60 patients were enrolled in the study, and inclusion criteria were age over 18 years, positive PCR test result, pulmonary involvement in computed tomography (CT) scan, and SpO_2 level below 93%. Individuals were divided into two control (hydroxychloroquine + lopinavir/ritonavir [Kaletra]) and intervention (hydroxychloroquine + lopinavir/ritonavir [Kaletra] + interferon-β 1a [recigen]) groups. The data were analyzed in Stata/SE 14.2 using Chi-square, *t*-test, and Mann-Whitney *U* test.

RESULTS: The mean ± standard deviation (SD) age of patients was 63 ± 16.12 years and 43.3% were male. In terms of outcome variables, 20% of patients in the intervention group and 53.3% of subjects in the control group died and this difference was significant ($P = 0.007$). According to the quick sequential organ failure assessment (qSOFA) score, the severe cases were 16.7% in the intervention group and 50% in the control group ($P = 0.006$). In addition, the median days of hospitalization were 11.5 days—significantly higher than those in the control group (5.5 days) ($P < 0.001$).

CONCLUSION: Based on the results of this study, the use of interferon in the treatment of COVID-19 can improve health and reduce the severity of the disease and mortality.

Keywords:

ARDS, COVID-19, inflammatory markers, interferon, treatment

Introduction

Coronavirus disease-2019 (COVID-19) is one of the main problems of the health and medical community, which suddenly started in December 2019 in Wuhan and it has spread rapidly around the world. The disease is officially named COVID-19 by the World Health Organization (WHO), and the SARS-CoV-2 virus is responsible for its infection.[1-3]

The most common clinical symptoms include respiratory symptoms such as fever and cough, and, in some patients, acute respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, and other severe complications along with other symptoms such as headache, heart problems, and fatigue.[4,5] In some studies, lung perforation has been reported during pathological evaluation. It was reported that ARDS and multiple organ damage such as cardiovascular system involvement are the most common causes of death in patients with COVID-19.[6]

Because of the onset of the COVID-19 pandemic, no definitive treatment has been introduced for the disease and efforts are

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ongoing to find effective treatments. However, various therapies including antiretroviral drugs, antimalarial drugs, favipiravir, remdesivir, corticosteroids, immunoglobulin, and cytokine blockers have been reported as adjunctive therapies for COVID-19.[7,8]

During infection with other types of viruses, host rescue is a key factor that mediates cellular innate antiviral immune response, and the SARS-CoV-2 virus is no exception. Although the biology, life cycle, and pathogenesis of different viruses are widely different, IFNs activate protective mechanisms aimed at controlling and eradicating the virus. According to previous studies, IFNs can be used for the prevention as well as early treatment of viral infections. It is used as a supplement to compensate for the inadequate production or activity of IFN that may be actively blocked by the virus.[9] So far, several studies have been performed to evaluate the effect of interferon in the treatment of COVID-19. In a clinical trial conducted by Rahmani *et al*.,[8] the effect of IFN β-1b in the treatment of patients with severe COVID-19 was investigated. According to the results of this study, the use of IFN β-1b reduced the time of clinical progression without side effects in patients with severe forms of the disease. It also reduced intensive care unit (ICU) hospitalization and the need for invasive mechanical ventilation in these patients.

In a cohort study conducted by Zhou *et al*.,[10] treatment of COVID-19 patients with IFN-α2b showed that the use of IFN-α2b significantly reduced the detection time of the virus in the upper airways and, at the same time, reduced the blood levels of IL-6 and C-reactive protein (CRP) inflammatory markers. The effect of IFNβ-1a on COVID-19 patients was investigated in a clinical trial conducted by Bosi *et al*.[11] in Italy. The results showed that the use of IFNβ-1a reduced the length of hospital stay and/or improved the clinical condition, making it a potential cornerstone in the treatment of COVID-19. It seems that the use of interferon can be effective in the treatment of COVID-19; however, there are still not enough studies to confirm this, and more studies are needed. Therefore, in this study, we aimed to investigate the therapeutic potential of interferon against COVID-19.

Materials and Methods

Study design and setting

This was a quasi-experiment with a nonequivalent group design. The target population was all admitted patients in Shahid Beheshti Hospital, Qom province.

Study participants and sampling

The study population was 60 patients with ages over 18 years, positive PCR test results, pulmonary involvement in computed tomography (CT) scan, and SpO_2 level below 93%. Individuals were divided into two control (hydroxychloroquine + lopinavir/ritonavir [Kaletra]) and intervention (hydroxychloroquine + lopinavir/ritonavi [Kaletra] + interferon-β 1a [recigen]) groups. Hydroxychloroquine and lopinavir/ritonavir (Kaletra) were consumed according to national guidelines published by the Ministry of Health and Medical Education, which were available at the time of the study (5th edition).[12] One 200 mg hydroxychloroquine oral tablet every 12 h up to 14 days. Two 50/200 mg lopinavir/ritonavir (Kaletra) oral tablet every 12 h up to 14 days. Also, 44 μg of interferon-β 1a (ReciGen) subcutaneously every other day, five doses. Other supportive measures such as acetaminophen, prophylactic anticoagulant, hydration, and oxygen therapy were prescribed based on the patient's clinical condition. The assignment was conducted by self-selection so that the researcher by going to the patient's bedside and explaining the study to him/her (in a fully conscious state) or his/her caretaker (in a non-fully conscious state), inquiring about the patient's desire to receive interferon. If the patient was willing to receive the interferon, he was in the intervention group and otherwise in the control group. All subjects were enrolled after signing the informed consent form.

Data collection tool and technique

After the patient was hospitalized, required data were extracted from the clinical record and hospital database and recorded in a researcher-made checklist. The checklist included five sections: 1-Demographic variables (age, gender), 2-History of underlying diseases (ischemic heart disease [IHD], obstructive airway disease [OAD], kidney disease, blood pressure [BP], and diabetes [DM]), 3-Vital signs (peripheral blood oxygen saturation [SpO2], respiratory rate [RR], heart rate [HR], systolic blood pressure [SBP], body temperature [T], and change in mental status [GCS]), 4-Laboratory parameters (white blood cells [WBCs], hemoglobin [Hb], creatinine [Cr], and CRP), and 5-Outcomes (mortality, number of hospitalization days, and quick sequential organ failure assessment [qSOFA] score). It is notable that laboratory parameters and qSOFA were collected two times, on the first day of hospitalization and the day of expiration/discharge.

The qSOFA consisted of three parameters: SBP, RR, and GCS, and its score were determined by summing the scores of three variables. If the sum was 0 or 1, the severity of the disease had considered low risk and if it was 2 or 3, had considered high risk.[13] Scoring was according to Table 1.

In this study, the data were statistically analyzed using Stata/SE 14.2. Categorical variables are described by frequency (frequency percentage) and were analyzed

using the Chi-square test. Continuous variables with normal distribution were described by mean (standard deviation [SD]) and were analyzed using a *t*-test and continuous variables with non-normal distribution were described by median (interquartile range [IQR]) and were analyzed using Mann-Whitney *U* test. The normal distribution of variables was assessed using the Shapiro-Wilk test. $P < 0.05$ was considered a significance level in all analyses.

Ethical consideration

The study was done in accordance with the Declaration of Helsinki version 2013, and the identification of participants was not disclosed.

Results

The mean ± standard deviation (SD) age among all participants was 63 ± 16.12 years, and 43.3% of patients were male and 73.3% had a history of underlying disease. Hypertension (41.7%) and diabetes (41.7%) were the most common underlying diseases[Table 2].

Table 1: Quick sequential organ failure assessment (qSOFA)

Parameter	Score
SBP	
≤100 mmHg	1
>100 mmHg	0
RR	
≥22/min	1
<22/min	0
GCS	
≤15	1
>15	0
Score range	0-3

In terms of vital signs, the median (IQR) of SpO_2, RR, SBP, and T of patients was 89% (85.5-92), 20 bpm (18-22), 37.50°C (37-38), 118 mmHg (110-130), and 37.5°C (37-38), respectively. The mean ± SD heart rate was 91.4 ± 14.9 bpm. The qSOFA score showed that the disease was severe in 21.67% of patients [Table 2].

In the survey of laboratory parameters, the median (IQR) of WBC, Cr, and CRP of the individuals were 6600 × 109/L (4450-11100), 1.1 mg/dL (0.9 –1.5), and 41 mg/dL (22 –52.5), respectively. The mean ± SD Hb was 12.6 ± 2.6 g/dL [Table 2].

Although in this study grouping was based on patient preferences rather than randomization, the distribution of patients in terms of variables affecting outcomes such as demographic variables, vital signs, disease severity, and laboratory parameters was the same in both groups and there was no significant difference ($P > 0.05$). Details of the results of the comparison of variables between the study groups are given in Table 2.

Evaluation of the mortality outcomes, the qSOFA score, and the number of hospitalization days showed a significant difference between the two groups. Twenty percent of patients in the intervention group and 53.3% of subjects in the control group died and this difference was significant ($P = 0.007$). The qSOFA score demonstrated the severe cases were 16.7% in the intervention group and 50% in the control group ($P = 0.006$). However, this value was 30% in the intervention group and 13% in the control group on the first day of admission. Finally, the median of the number of hospitalization days (11.5 days) was significantly higher than that of the control group (5.5 days) ($P < 0.001$) [Table 3].

Table 2: Participants' characteristics on the first day of hospitalization

Variables	Total (*n*=60)	Intervention (*n*=30)	Control (*n*=30)	*P*
Age (year), Mean (SD)	63 (16.2)	63.1 (16.2)	62.8 (16.4)	0.937
Gender (male vs female), *n* (%)	26 (43.3)	13 (43.3)	13 (43.3)	1.000
Underlying disease (yes vs. no), *n* (%)	44 (73.3)	23 (76.7)	21 (7)	0.559
BP (yes vs. no), *n* (%)	25 (41.7)	12 (40)	13 (43.3)	0.793
DM (yes vs. no), *n* (%)	25 (41.7)	12 (40)	13 (43.3)	0.793
IHD (yes vs. no), *n* (%)	20 (33.3)	10 (33.3)	10 (33.3)	1.000
OAD (yes vs. no), *n* (%)	4 (6.7)	3 (10)	1 (3.3)	0.301
Kidney disease (yes vs. no), *n* (%)	3 (5)	3 (10)	0 (0)	0.076
SPO2 (%), median (IQR)	89 (85.5-92)	90 (88-92)	88 (80-92)	0.068
RR (bpm), median (IQR)	20 (18-22)	20 (18-20)	20 (18-24)	0.061
HR (bpm), mean (SD)	91.4 (14.9)	89.6 (13)	93.1 (16.7)	0.373
SBP (mmHg), median (IQR)	118 (110-130)	116 (110-128)	120 (110-130)	0.876
T (°C), median (IQR)	37.5 (37-38)	37.7 (37-37.9)	37.4 (36.9-38.1)	0.662
qSOFA (high-risk vs. low-risk), *n* (%)	13 (21.7)	9 (30)	4 (13.3)	0.117
WBC ($\times 10^9$/L), median (IQR)	6600 (4450-11100)	5600 (3800-9800)	7450 (4800-12500)	0.151
Hb (g/dL), mean (SD)	12.6 (2.6)	12.6 (2.5)	12.6 (2.7)	0.938
Cr (mg/dL), median (IQR)	1.1 (0.9-1.5)	1.1 (0.9-1.4)	1.2 (0.9-1.5)	0.458
CRP (mg/dL), median (IQR)	41 (22-52.5)	36 (9-52)	49.5 (33-54)	0.025

Although on the first day of hospitalization, there was no significant difference in the distribution of laboratory parameters between the two groups [Table 2], after treatment, a significant difference in CRP ($P < 0.001$) was observed [Table 4]. In addition, plasma CRP levels decreased in both groups (from 36 to 12 in the intervention group and from 49 to 33 in the control group), which was more remarkable in the intervention group.

Discussion

The aim of this study was to evaluate the effect of interferon in the treatment of COVID-19. The findings showed that the use of interferon in the treatment of COVID-19 is effective in controlling the disease and reducing its severity. Of the 60 COVID-19 patients who were enrolled in the study, some of them had a history of underlying diseases including hypertension, diabetes, ischemic heart disease, obstructive airways, and renal disease. Based on secondary qSOFA (16.67 vs. 50), a lower incidence of severe cases was found in the intervention group compared with the control group, which indicates that interferon is effective in controlling COVID-19. During the treatment with interferon, a reduction in the disease severity in the intervention group (high-risk qSOFA from 30 to 16.67) occurred. No reduction in the term of disease severity was found in the control group (high-risk qSOFA from 13.33 to 50).

In the study conducted by Davoodi *et al*.,[12] the efficacy and safety of IFN β-1a in the treatment of severe COVID-19 were investigated. Of the 42 severe cases of COVID-19 patients who received IFN β-1a, no significant difference was found between this group and the control group who received standard medication according to a national protocol (including hydroxychloroquine together with lopinavir–ritonavir, or atazanavir-ritonavir). According to the finding, on day 14, 66.7% and 44.6% of patients in the interferon and the control group were discharged, respectively. Also, mortality on day 28, was significantly lower than that in the control group. In another study by Rahmani *et al*.,[8] the effect of IFN β-1b in the treatment of severe COVID-19 was investigated in 33 severe cases of COVID-19 patients. The results of a study showed that the duration of disease progression was significantly lower in the interferon group than in the control group. On day 14, the percentage of discharged patients was 78.79% and 54.55% in the interferon and control groups, respectively. The time of ICU admission in the control group was significantly higher than that in the interferon group. There was no significant difference between the length of hospital stay and ICU admission in the two groups. Mortality on day 28 was reported to be 6.06% and 18.18% in the interferon and control groups, respectively.

Wang *et al*.[13] conducted a study and investigated the relationship between early interferon therapy and appropriate clinical response in COVID-19 patients. They enrolled 442 COVID-19 patients in the retrospective cohort study. The results showed that early administration of interferon (≤5 days of hospitalization) reduced in-hospital mortality compared to those who did not receive interferon. Delayed administration of interferon was associated with increased mortality. Among those who recovered, early interferon administration was not associated with the time of hospital discharge or progression on CT scan, whereas late administration was associated with delayed recovery.[14]

As mentioned, several studies have been conducted to evaluate the effect of interferon in the treatment of COVID-19 patients and highlighted its effectiveness. Most findings are consistent with the findings of the present study. The results of this study showed that the length of hospitalization time in the intervention group was significantly longer than that in the control group. This was also observed in ICU subgroups. One of the most important reasons for this is the higher percentage of recovered patients in the intervention group than in the control group (80% vs. 46.67%). Higher mortality and fewer cases of recovery in the control group were also among the causes that led to a longer hospital stay

Table 3: Comparison of outcomes among studied groups

Outcomes	Total (*n*=60)	Intervention (*n*=30)	Control (*n*=30)	*P*
Mortality (expired vs. discharged), *n* (%)	22 (36.7)	6 (20)	16 (53.3)	0.007
qSOFA score* (high-risk vs. low-risk), *n* (%)	20 (33.3)	5 (16.7)	15 (50)	0.006
Hospitalization (day), median (IQR)	8 (5-14.5)	11.5 (7-18)	5.5 (4-8)	<0.001

*At the discharged or expired day

Table 4: Comparison of laboratory parameters on the day of expired/discharged

Variables	Total (*n*=60)	Intervention (*n*=30)	Control (*n*=30)	*P*
WBC ($\times 10^9$/L), median (IQR)	9900 (7200-13100)	9700 (7400-13700)	10150 (6900-13100)	0.982
Hb (g/dL), mean (SD)/median (IQR)	11.8 (10.5-13.3)	11.1 (10.2-13.3)	11.9 (11.1-13.2)	0.133
Cr (mg/dL), median (IQR)	1.0 (0.9-1.4)	0.9 (0.9-1.2)	1.1 (0.9-1.8)	0.197
CRP (mg/dL), median (IQR)	20 (11.5-37.5)	12 (4-22)	33 (18-48)	<0.001

in the intervention group compared with the control group. However, studies are still not enough and more studies with large populations seem to be necessary for demonstrating its effectiveness in the treatment of COVID-19.

Conclusion

Since the outbreak of COVID-19, various treatments have been used for the treatment of these diseases. The treatment, which offers a low mortality rate in infected patients is of great importance. The use of interferon is introduced in several studies that have revealed its effectiveness in the treatment of COVID-19. This effectiveness was also highlighted in our study; early administration of interferon offers a low mortality rate with an increased time of hospitalization in the population compared with the control group. However, according to the findings of this research, we conclude that interferon can be considered a good alternative agent with promising therapeutic indexes for COVID-19.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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