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Investigating the Therapeutic Effect of β-Interferon and Methylprednisolone on COVID- 19 Patients' Consequence: A Non- Randomized, Double-Blinded, Controlled Study

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ABSTRACT

Background & Objective: Due to the severe inflammatory conditions and cytokine storm in COVID-19 disease, corticosteroids are used worldwide as adjunctive therapy for these patients due to their anti-inflammatory effects. However, due to limited and inconsistent information about the effectiveness of this drug, this study aimed to investigate the benefit of combined use of β-interferon and methylprednisolone in patients with COVID-19.

Materials & Methods: 57 patients infected with SARS coronavirus 2 underwent treatment. Laboratory parameters, hospitalization duration, and clinical outcomes in these patients were studied.

Results: Statistical analysis showed no correlation between combination therapy with the hospitalization duration (P=0.22) and mortality (P=0.48). Also, the findings of this study showed that the ESR level in patients receiving combination therapy with methylprednisolone and interferon beta decreased significantly at the end of the intervention (P=0.0001). At the end of the study, the levels of neutrophils (P=0.001) and lymphocytes (P- value=0.0001) in the blood in the interferon group showed a significant change.

Conclusion: This study showed no effect of adding methylprednisolone and interferon beta to the treatment protocol on mortality in the patients.

Keywords: COVID-19, Methylprednisolone, Interferon-beta, SARS-CoV-2

Introduction

Since late December 2019, severe Coronavirus 2 (SARS-COV-2) acute respiratory syndrome infection has spread rapidly worldwide. And as of 26 December 2020, there have been 78,604,532 cases and 1,744,235 deaths worldwide according to the World Health Organization (WHO). Although the majority of COVID-19 patients have a mild and self-limiting illness, the viral infection becomes critical in about 5% of patients and progresses to severe pneumonia, acute respiratory syndrome, limb dysfunction, and eventual death. There are many related issues in health care systems. Despite much in vitro research, there is currently no effective or proven vaccine or drug to treat COVID-19 patients.

Studies have shown that the increased production of pro-inflammatory and inflammatory cytokines in patients with severe SARS-COV-2 pneumonia, leads to inflammatory responses. This results in the activation of platelets, neutrophils, monocytes, macrophages, destruction of airway, pathways and alveolar damage, leading to respiratory failure. This occurs in patients within 5-7 days, and in severe cases, it leads to acute respiratory failure and death (4-6). Therefore, it seems that using a method to contain the pro-inflammatory response and prevent overproduction of cytokines at this stage is of great importance (4, 5).

High doses of corticosteroids, due to their anti-inflammatory, anti-fibrotic, and cytokine response effects, can be used to suppress the systemic inflammatory response syndrome and prevent lung damage from severe pneumonia. On the other hand, some studies have shown that the use of these drugs may cause potential side effects in COVID-19 patients due to the possibility of impaired immune responses caused by sepsis (7). Therefore, some researchers believe that the drug use of corticosteroids to treat coronavirus is ineffective (8). However, the development of clinical complications in patients is strongly related to the disease, the time of intervention, the dose of the drug, and the duration of treatment, and requires further studies in this field (9). Studies have shown that although the use of low-dose corticosteroids does not reduce mortality from septic shock in lung infections, it can improve some clinical outcomes (10). Furthermore, many studies have shown the effectiveness of corticosteroids in patients with ARDS, that can reduce

mortality in patients with H1N1, and improve many of the symptoms of SARS in patients (11). Methylprednisolone is a synthetic glucocorticoid that suppresses the immune system and is important for stopping or delaying the progression of pneumonia. It has been shown to be effective in treating acute respiratory distress syndrome (ARDS). Studies have shown that using this drug in high doses can potentially reduce the inflammatory response (12). A recent study showed that although the mortality rate is high in COVID-19 patients treated with methylprednisolone, the utilization of this corticosteroid seems to decrease the risk of death in patients with COVID-19 pneumonia who suffer from acute respiratory distress (8, 13). In addition, the findings of an experimental study showed that IL-6 levels decreased continuously after the combined administration of Tocilizumab and methylprednisolone (4).

Given many unanswered concerns and questions about the clinical use of corticosteroids such as methylprednisolone as adjunctive therapy for COVID-19 pneumonia, a double-blind, non- randomized, clinical trial is required to determine the dose and duration of Methylprednisolone use and to determine the most effective treatments for COVID-19. Therefore, to address this issue and evaluate the efficacy, safety, and clinical use of combination therapy with interferon beta and methylprednisolone for SARS-CoV-2 infection, the results of a non- randomized ,controlled clinical trial in COVID-19 patients with two case groups are presented.

Materials and Methods

Study design and participants:

This double-blind, non- randomized, controlled trial was performed to investigate the efficacy and safety of combination therapy of interferon beta and methylprednisolone in adult patients who referred to Shahid Sadoughi Hospital in Yazd. Between January 21, 2020, and March 19, 2020, 57 patients with COVID-19 were enrolled according to the inclusion criteria. All participants in this study were positive for RT-PCR. Forty three patients were assigned to the interferon group and 14 patients received interferon and methylprednisolone. Using throat swap samples at the beginning of the study and reverse transcriptase polymerase chain reaction (rt-PCR) method, COVID-19 diagnosis was confirmed. In addition, the patients underwent blood tests and high resolution CT. Eligible participants in this study were adults (18 years and older) with COVID-19 based on the findings of High Resolution Computed Tomography (HRCT). They also had progressive and severe hypoxia (lower than 88% blood oxygen saturation with a reservoir bag mask and flow of 15 liters) and a decrease in lymphopenia. The exclusion criteria were history of cardiovascular disease, liver cirrhosis (grade 3 and above), history of renal failure, severe depression, autoimmune diseases, organ transplantation, and pregnancy or lactation. Sample size was calculated with the formula provided for parallel clinical trials, considering type 1 error (α) of 0.05, type 2 errors (β) of 0.2, and 20% attrition rate; the final calculated sample size was 27 participants per group.

The experimental protocol was approved by the Ethics Committee of Shahid Sadoughi Hospital in Yazd (IR.SSU.REC.1399.040). All participants or their legal representatives gave informed written consent. Each patient was assigned a code and his/her information was stored on an encrypted computer. The clinical trial was performed in accordance with the principles of the Helsinki Declaration, whose protocol is available online (http://www.wma.net/en/30publications/10policies/b3/index.html). The research was in accordance with the CONSORT statement. Trial registration: irct.ir Identifier: IRCT20200825048514N1.

Blinding:

The blinding was executed without the patients' knowledge about the type of treatment and with the consent of each patient's family. An independent statistical expert from the survey team allocated eligible patients in a 1: 1 ratio to the interferon beta and methylprednisolone combination group or the interferon beta group. An independent pharmacist from the experimental team (from the pharmacy of Shahid Sadoughi Hospital) marked the labels with the study ID on distinct numbered packages for the combined treatment of interferon beta, methylprednisolone and interferon beta based on a randomization list (M & C codes). None of researchers, clinical and laboratory personnel, and contributors were informed of the kind of treatment devoted to each individual. Only the pulmonologist responsible for each patient was aware of the type of treatment. The course of recording blood oxygen saturation percentage, body temperature, respiratory rate, lymphopenia, etc. was performed by nurses without knowing the type of treatment.

Method of intervention:

The demographic information, disease history, clinical and laboratory parameters for each patient were measured at the beginning of the study and recorded in the medical history of each patient (Table 1).

Body temperature, blood pressure, respiration rate (RR), heart rate, and O2 saturation (O2sat) of each patient were recorded and measured by nurses from the beginning of the study to the final result. The safety assessments included daily monitoring for side effects, clinical laboratory tests during each patient's hospital stay, and measurement of vital signs on a daily basis. The data recorded in each patient's file were entered into a computer and analyzed by the researchers. The mean O2sat at rest upon admission was not remarkably different in the two groups. All 57 patients were treated with oxygen.

Table 1. **Baseline Characteristics of Study Participants**

Variables	Interferon andpulse Medrol Group (N=14)	Interferon Group (N= 43)	P-value
personal feature			
Age (year)	66.85 (± 18.43)	63.90 (± 16.27)	0.57
Sex (M), n (%)	7 (50%)	33 (76.7%)	0.08
Vital signs at the beginning of the study			
Systolic blood pressure (mm Hg)	122.92 (± 25.95)	123.33 (± 18.54)	0.95
Diastolic blood pressure (mm Hg)	77.61 (± 14.86)	74.44 (± 11.58)	0.43
Pulse rate (bpm)	83.84 (± 10.84)	84.91 (± 11.74)	0.77
O2 saturation, %	86.50 (± 7.56)	87.18 (± 9.00)	0.79
Comorbidities (Disease History), n (%)			
Heart Disease	1 (7.1%)	9 (20.9%)	0.227
Lung Disease	1 (7.1%)	4 (9.3%)	0.643
Diabetes	5 (35.7%)	19 (44.2%)	0.408
HTN	4 (28.6%)	18 (41.9%)	0.288
HLP	2 (14.3%)	3 (7%)	0.357
laboratory			
WBC	5.67 (± 1.68)	10.43 (± 12.23)	0.16
Nut	73.20 (± 9.17)	79.14 (± 9.87)	0.05
Lymphocytes	21.09 (± 8.03)	15.44 (± 8.86)	0.04
PLT	171.57 (± 79.36)	190.17 (± 82.40)	0.46
ESR, mm/ h	68.78 (± 27.30)	58.25 (± 27.12)	0.24
Respiratory Rate, breaths per min	19.85 (± 2.82)	20.87 (± 5.80)	0.43
Temperature, ºC	37.66 (± 0.82)	37.25 (± 0.82)	0.11

-Values reported as mean (± SD) or counts (percentages). Independent samples t-test (2-tailed).
-Abbreviations: M: Male; bpm: beats per min; HTN: Hypertension; HLP: Hyperlipidemia; WBC: White blood cell; Nut: Neutrophils; PLT: Platelets; ESR: Erythrocyte Sedimentation Rate.

The blood samples were collected from each patient for biochemical evaluation at the beginning of the study and during hospitalization days. The serum levels of White Blood Cell (WBC), Nut, Lym (Lymphocyte), ESR (Erythrocyte Sedimentation Rate), CRP (C-Reactive Protein) and PLT (Platelet) were measured daily for each patient by trained nurses. The national treatment and intervention protocol were adopted based on the choice of the study methodologist for each patient and was announced to the pulmonologist. This study was performed on the first wave of coronavirus when antiviral drugs other than hydroxychloroquine and Kaletra were not available. Both groups received Kaletra 400 mg every day (morning and night), Naproxen 250 mg daily (morning and night) and one dose of 400 mg Hydroxychloroquine on the first day of hospitalization according to the national treatment protocol. For the intervention group, 500 mg methylprednisolone was given weekly and 0.44 mg β- interferon was administered subcutaneously every day. The control group received 0.44 mg of β- interferon subcutaneously every day. The nurses were asked to record any side effects and notify the pulmonologist about them.

Statistical analysis:

Statistical analysis was performed by SPSS software version 23 (SPSS Inc., Chicago, USA). Data were presented as mean ± standard deviation (SD). P- Value less than 0.05 was regarded statistically considerable. In this investigation, chi-square and independent samples t-test were used to compare the variables between the two groups before the intervention. Also, analysis of variance (ANOVA) was applied to compare the changes of each variable between the two groups at end of the intervention.

Results

Characteristics of participants:

Demographic characteristics, comorbidities, vital signs, and laboratory parameters of the studied patients at the time of admission are shown in Supplementary

Table 1. Baseline characteristics were similar in the methylprednisolone and control groups. The means of age of patients in the interferon and the interferon and methylprednisolone groups were 63.90 (± 16.27) years and 66.85 (± 18.43) years respectively. The sex distribution was 33 (76.7%) males versus 10 (23.3%) females in the interferon group and 7 (50%) males versus 7 (50%) females in the intervention group (Table 1). In the intervention group, 1 patient (7.1%) had cardiovascular disease, 1 patient (7.1%) lung disease, 5 patients (35.7%) diabetes, 4 patients (28.6%) hypertension and 2 patients (14.3%) had hyperlipidemia while the numbers of these patients in the interferon group were 9 (20.9%), 4 (9.3%), 19 (44.2%), 18 (41.9%) and 3 (7%), respectively. There was no remarkable difference in the frequency of underlying disease in patients in the intervention and control groups (Table 1). None of the subjects in the two study groups were smokers.

Radiology results:

As shown in Table 2, in radiographic imaging, 8 patients (57.1%) in the intervention group and 32 patients (74.4%) in the interferon group had bilateral penetrations into the lungs. The results of the chest CT scan in patients of both groups are given in Table 2. No considerable differences were detected between the two groups at the beginning of the study.

Table 2. Image features and lung involvement in the two groups

Variables		Interferon and pulse Medrol Group (N=12)	Interferon Group (N= 34)	P-value
Lung infiltrates zone	Lower	1 (7.1%)	3 (7%)	0.52
	Lower and Middle	2 (14.3%)	2 (4.7%)	
	Diffuse	9 (64.3%)	29 (67.4%)	
Variables		**Interferon and pulse Medrol Group (N=8)**	**Interferon Group (N= 34)**	**P-value**
Chest imaging, infiltrate*	**Unilateral involvement**	-	2 (4.7%)	0.652
	Bilateral involvement	8 (57.1%)	32 (74.4%)	

- Values reported as counts (percentages). Independent samples t-test (2-tailed).
- Values reported as frequency (percentages). Fisher´s Exact Test.
* Chest x-ray and computed tomography scan.

Laboratory indicators:

At the end of the study, CRP levels were 1.83 (± 1.60) in the interferon group and 1.00 (± 00) in the interferon and methylprednisolone groups. Other laboratory findings are summarized in Tables 3, 4 and 5. As Table 4 shows, the ESR level in patients receiving combination therapy with methylprednisolone and interferon decreased significantly at the end of the intervention (P = 0.0001). At the end of the study, the levels of neutrophils and lymphocytes in the blood in the interferon group showed a significant change (see Table 5)

Table 3. Effect of combination of interferon and pulse medrol versus interferon intervention on COVID- 19 related markers between the two groups after the intervention.

Variables	Interferon and pulse Medrol	Interferon	P-value*
Respiratory Rate, breaths per min	18.85 (± 3.63)	21.00 (± 6.39)	0.252
Temperature, ºC	37.17 (± 0.91)	37.16 (± 0.63)	0.943
O2 saturation, %	91.21 (± 5.04)	91.04 (± 5.48)	0.917
WBC	12.23 (± 11.08)	10.27 (± 5.26)	0.92
Nut	78.57 (± 13.83)	82.01 (± 12.18)	0.389
Lymphocytes	15.50 (± 10.71)	11.61 (± 9.12)	0.20
PLT	239.85 (± 112.09)	209.33 (± 115.67)	0.397
ESR, mm/h	40.00 (± 14.14)	68.77 (± 38.60)	0.342

- Data are presented as mean (± SD). *Independent t-test (2-tailed).
- WBC: White blood cell; Nut: Neutrophils; PLT: Platelets; ESR: Erythrocyte Sedimentation Rate.

Table 4. Effect of combination of interferon and pulse medrol intervention on COVID- 19 related markers after the intervention.

Variables	Baseline	After intervention	Change*	P-value**
Respiratory Rate, breaths per min	19.85 (± 2.82)	18.85 (± 3.63)	1.00 (± 1.36)	0.42
Temperature, ºC	37.66 (± 0.82)	37.17 (± 0.91)	0.48 (± 29)	0.456
O2 saturation, %	86.5 (± 7.56)	91.21 (± 5.04)	-4.71 (±2.16)	0.448
WBC	5.67 (± 1.68)	12.23 (± 11.08)	-6.55 (±3.05)	0.673
Nut	73.20 (± 9.17)	78.57 (± 13.83)	-5.37 (±4.75)	0.583
Lymphocytes	21.09 (± 8.03)	15.50 (± 10.71)	5.59 (±3.67)	0.85
PLT	171.57 (± 79.36)	239.85 (± 112.09)	-68.28 (±32.00)	0.380
ESR, mm/h	68.78 (± 27.30)	40.00 (± 14.14)	19.00 (±11.00)	0.0001

- *Data are presented as mean (± SEM). ** paired t-test.
- WBC: White blood cell; Nut: Neutrophils; PLT: Platelets; ESR: Erythrocyte Sedimentation Rate.

Table 5. Effect of interferon intervention on COVID- 19 related markers after intervention.

Variables	Baseline	After intervention	Change*	P-value**
Respiratory Rate, breaths per min	20.87 (± 5.80)	21.00 (± 6.39)	-0.46 (±1.58)	0.343
Temperature, ºC	37.25 (± 0.82)	37.16 (± 0.63)	0.093 (±0.162)	0.725
O2 saturation, %	87.18 (± 9.00)	91.04 (± 5.48)	-3.86 (±1.44)	0.173
WBC	10.43 (± 12.23)	10.27 (± 5.26)	0.52 (±2.07)	0.162
Nut	79.14 (± 9.87)	82.01 (± 12.18)	-2.08 (±1.72)	0.001
Lymphocytes	15.44 (± 8.86)	11.61 (± 9.12)	3.46 (±1.18)	0.0001
PLT	190.17 (± 82.40)	209.33 (± 115.67)	-15.51 (±19.28)	0.05
ESR, mm/h	58.25 (± 27.12)	68.77 (± 38.60)	-2.16 (±15.26)	0.507

- *Data are presented as mean (± SEM). ** P-value was obtained by paired t-test.
- WBC: White blood cell; Nut: Neutrophils; PLT: Platelets; ESR: Erythrocyte Sedimentation Rate.

Clinical data:

Clinical findings show that 9 patients in the intervention group (64.3%) and 23 patients (53.5%) in the control group improved and were discharged from the hospital. The length of hospital stay in the group receiving interferon and methylprednisolone combination therapy was 12.07 (± 5.16) days, while it was 9.88 (± 5.96) days in the control group. Although the length of the hospital stay was longer in the interferon group, the difference between the groups was not considerable (P = 0.22).Five patients (35.7%) in the intervention group, and 20 patients (46.5%) in the control group, died during hospitalization. The results of this study show that there was no significant difference in mortality between the two groups (35.7% versus 46.5%; P= 0.479).

Discussion

In this non-randomized, controlled clinical trial, methylprednisolone intake was evaluated in patients with COVID-19 in Yazd. The results showed that there was no significant difference between the two groups in terms of mortality rate and survival improvement at the end of the study.

The results of studies using corticosteroids in the COVID-19 patients recovery are contradictory. However, the findings of this study are in line with many studies in this field. A cohort study conducted by Yin Wang et al., in 2020 to treat methylprednisolone in severe patients with COVID-19 pneumonia in 46 patients concluded that there is no serious risk from using methylprednisolone and antibacterial drugs should be used if a secondary infection develops following the use of methylprednisolone. In this study, there was no significant difference in mortality between the methylprednisolone treatment and control groups, however, in patients receiving methylprednisolone, the length of hospital stay in the ICU was shorter and chest CT scan findings were significantly better (5).

Findings from many studies have shown that although low-dose or physiological use of corticosteroids do not reduce mortality from primary

lung infections and have no significant effect on the clinical course of COVID-19 pneumonia , they can have beneficial effects on some secondary clinical outcomes such as lymphocyte count and CRP, shorter ICU stay, and mechanical ventilation **(14-17)**.

Other studies have shown that the use of corticosteroids in patients with COVID-19 does not significantly reduce mortality in this group of patients **(18-20)**.

However, some studies have shown a positive effect of corticosteroid use in patients with COVID-19. Results from a study of elderly patients with Covid-19 showed that steroid therapy improved clinical outcomes. This may be due to higher CRP levels in these people **(21)**.

Another study showed that dexamethasone reduced mortality in the patients with severe COVID-19 **(18)**. A meta-analysis showed that corticosteroid in patients with COVID-19 was associated with reduced mortality **(22)**. Besides, a cohort study showed that treatment with methylprednisolone may be beneficial for patients with ARDS and reduce the risk of mortality in this group of patients **(13)**.

In a 2020 study by Wei Zhou et al., on 15 patients with new coronavirus pneumonia for determining the effectiveness of corticosteroid therapy, it was found that the use of corticosteroids in the first 3-5 days increases oxygen saturation. The use of these drugs in a group of patients with COVID-19 had potential therapeutic benefits **(8)**. Therefore, to confirm our findings, it is necessary to conduct a systematic review and meta-analysis.

Conclusion

In summary, this study indicates that the combination of methylprednisolone and interferon in patients with COVID-19 did not have a significant effect on laboratory parameters and mortality compared with the control group. A confirmed randomized, controlled, clinical trial with a larger sample size is necessary to confirm these results.

Limitations and strengths of the study

The limitations of this study are stated below. The study was conducted in a single- referral center so the findings generalizability is limited. Also, all patients CT scans were not reported by the same radiologist. Therefore, to confirm these findings, further investigations can evaluate the effect of methylprednisolone on the long-term clinical outcome of patients with COVID-19 with a large sample size that represents the entire population. One of the strengths of the present study was blinded nature of the research along with a control group.

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Conflict of Interest

The authors express that there are no competing interests.

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