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Original Article

Efficacy of naproxen in the management of patients hospitalized with COVID-19 infection: A randomized, double-blind, placebo-controlled, clinical trial

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ABSTRACT

Background and aims: The current study was done to examine the efficacy of naproxen in the management of patients with COVID-19 infection.
Methods: This randomized, double-blind, placebo-controlled, clinical trial was done on hospitalized adult patients with confirmed COVID-19 infection. Patients were randomly assigned to receive either naproxen (two capsules per day each containing 500 mg naproxen sodium) or placebo (containing starch) for five days along with the routine treatment that was nationally recommended for COVID-19 infection. Clinical symptoms of COVID-19 infection, the time to clinical improvement, blood pressure, laboratory parameters, and death due to COVID-19 infection were considered as the outcome variables in the present study.
Results: Treatment with naproxen improved cough and shortness of breath in COVID-19 patients; such that, compared with placebo, naproxen intake was associated with 2.90 (95% CI: 1.10−7.66) and 2.82 (95% CI: 1.05−7.55) times more improvement in cough and shortness of breath, respectively. In addition, naproxen administration resulted in a significant increase in mean corpuscular volume (MCV) and had a preventive effect on the reduction of systolic blood pressure in COVID-19 patients.
Conclusion: Treatment with naproxen can improve cough and shortness of breath in COVID-19-infected patients. Further studies are required to confirm our findings.

1. Introduction

The ongoing pandemic of COVID-19 infection, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been the major health concern in the world [1]. This infection has involved more than 13 million individuals and has led to 583,655 deaths until July 15, 2020 [2]. Most cases of COVID-19 are self-improved, however, about 5−15% of infected individuals show severe pneumonia, hypoxaemic respiratory failure, acute respiratory distress syndrome, and finally multi-organ failure [3]. These critically ill patients require supplemental oxygen via invasive mechanical ventilation [4]. Nevertheless, 50% of patients in an acute condition, who require mechanical ventilation, die in hospital [5]. Therefore, finding appropriate strategies for the treatment and management of COVID-19 patients is urgently required.

There are no effective antiviral medications for COVID-19 infection. At present, the prescribed drugs are usually used for alleviating disease complications and symptoms such as inflammation, fever, cough, chest pain, and respiratory distress [5−7]. Non-steroidal anti-inflammatory drugs (NSAIDs) including ibuprofen, diclofenac, aspirin, and indomethacin are commonly prescribed for this purpose [8,9]. Among NSAIDs, little attention has been laid on naproxen. In addition to anti-inflammatory properties, naproxen provides antiviral effects that may make it a good choice for viral respiratory infections [10]. Naproxen is a nonselective cyclooxygenase (COX) inhibitor, which reduces the production of

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inflammatory mediators such as prostaglandins [11].

Only two studies assessed the probable effects of naproxen in patients with viral respiratory infections [12,13]. In a randomized clinical trial (RCT), oral administration of naproxen (loading dose, 400−500 mg followed by 200−500 mg three times daily for 5 days) had no significant effect on virus shedding or serum neutralizing antibody responses; however, it could improve disease symptoms such as headache, malaise, myalgia, and cough [12]. In another RCT regarding COVID-19 infection, a combination of azithromycin, prednisolone, naproxen, and lopinavir/ritonavir decreased serum concentrations of C-reactive protein (CRP) and the average length of stay in hospitals (ALOS) in infected patients [13]. However, the individual effect of naproxen cannot be extracted from this RCT [13]. Overall, the effect of naproxen on COVID-19 infection and its symptoms is still unknown. Therefore, in the present RCT, we decided to examine the efficacy of naproxen in the management of hospitalized patients with COVID-19 infection.

2. Material and methods

2.1. Participants

This study was a randomized, double-blind, placebo-controlled, clinical trial that was done in Abadan, Iran, in 2020. We recruited hospitalized patients with COVID-19 infection from the Ayatollah Taleghani Hospital, Abadan, Iran. COVID-19 infection was diagnosed via chest computed tomography (CT) scan and was confirmed using the real-time polymerase chain reaction (RT-PCR) test of the nasopharyngeal sample. We included patients aged 18 years or older and those who were willing to participate in the current trial. Patients who were in pregnancy and lactation periods, those with a history of intestinal ulcers and gastrointestinal bleeding, those who were taking losartan and captopril, and patients with an age range of <18 years were not included. Also, we excluded patients during the trial if they changed the type or dosage of their medicines, died or were not willing to continue the intervention, and suffered from possible complications related to naproxen. The study flowchart is shown in Supplemental Figure 1.

All patients read the sentences written in the consent form and they could optionally accept to participate in the current study. The ethics committee of the Abadan School of Medical Sciences approved the study (with code of IR.ABADANUMS.REC.1398.115). Moreover, this study was registered in the Iranian Registry of Clinical Trials (www.irct.ir) on 2020-03-30 with the code number IRCT20200324046850N3.

2.2. Sample size calculation

On the basis of the following sample size formula designed for randomized clinical trials and considering the type I error of 5% ($\alpha = 0.05$), type II error of 20% ($\beta = 0.20$, power = 80%), and serum concentrations of CRP as the key variable, we required 30 patients for each group. However, by considering a 30% drop-out, we recruited 40 participants for each intervention group.

$$n = \frac{2[(a+b)^2 \times \sigma^2]}{(\mu_1 - \mu_2)^2}$$

n = sample size in each group
μ_1 = mean for serum concentrations of CRP in the intervention group.
μ_2 = mean for serum concentrations of CRP in the control group
σ = variance (SD) for mean concentrations of CRP (which was considered the greatest SDs reported for serum concentrations of CRP in the intervention and control groups.
a = conventional multiplier for alpha = 0.05 that was 1.96
b = conventional multiplier for power = 0.80 that was 0.842

The means and SD for serum concentrations of CRP were obtained from the study of Vahedi et al. [13].

2.3. Study design

After recruiting the patients with COVID-19 infection, they were randomly allocated to the naproxen or placebo groups using block randomization. To do block randomization, six patients were placed in a block, and then, the six patients in that block were randomly assigned to the naproxen and placebo groups. For randomization, an allocation code was given to each eligible patient and then, the codes of patients were stated in the lottery container, and finally, patients were randomly assigned to the naproxen or placebo groups. Random allocation was performed by a person who was unaware of the purpose of our study. Patients in the naproxen group received one naproxen capsule (containing 500 mg naproxen sodium) every 12 h along with the routine treatment that was nationally recommended for COVID-19 infection [Hydroxychloroquine Sulfate tablet, 200 mg every 12 h (Tehran Daroo), Kaletra tablets containing 50 mg Lupinavir and 200 mg Ritonavir, every 12 h (Indian Ritcomum)]. Patients in the placebo group received a placebo capsule (containing starch) every 12 h plus the routine treatment that was similar to the naproxen group. The intervention lasted for 5 days. Naproxen and placebo capsules were purchased from the Pars Daru Company in Iran. Placebo capsules were similar to the naproxen capsules in terms of appearance and color. To ensure the use of naproxen and placebo capsules, we recorded the time that patients took the capsule. In addition, participants' compliance was assessed using the following formula: (number of used capsules/all given capsules) × 100.

2.4. Assessment of variables

At baseline, information on age, gender, marital status, medical history, and smoking was collected using a standard questionnaire. Clinical symptoms of COVID-19 infection, blood pressure, O_2 saturation (Sao_2), and respiratory rate were assessed at baseline and days 2, 3, 4, and 5 of the intervention. Also, clinical and laboratory parameters were measured at baseline and the end of the intervention (day 5). The time to clinical improvement and death were assessed at baseline and the end of the intervention (day 5) as well as days 7, 14, 21, and 28 after the intervention.

2.5. Assessment of symptoms

A trained nurse assessed all patients once a day using diary cards that captured data on clinical symptoms of COVID-19 infection including cough, shortness of breath, fever, headache, myalgia, olfactory and taste disorders, night weats, trembling, and chest pain from baseline (day 1) to the end of the intervention (day 5). These assessments were done using clinical observation and examination or by an interview with the patients. Improvement rate was defined as the elimination of each symptom at day 5 compared with baseline. In addition to symptoms, data on respiratory rate, Sao_2, and blood pressure were recorded daily for each patient. Respiratory rate was considered as the number of breaths per minute. Sao_2 was measured using the pulse oximeter. Systolic and diastolic blood pressures were measured twice with a 15-min interval at the right arm using a mercury barometer calibrated by the Institute of

Standardization and Industrial Research. The average of two measurements was considered as participants' systolic and diastolic blood pressures.

2.6. Clinical improvement

The time to clinical improvement was evaluated using a seven-category ordinal scale that was recommended by the world health organization (WHO) for clinical trials performed on patients with severe influenza [14,15]. This scale consists of seven categories including: 1) not hospitalized with the 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 ECMO, invasive mechanical ventilation, or both; and 7) death [15]. The time to clinical improvement was defined as the time from baseline to an improvement of two points on the seven-category ordinal scale or live discharge from the hospital. Clinical improvement was assessed at baseline and the end of the intervention as well as days 7, 14, 21, and 28 after the intervention.

2.7. Biochemical assessment

A 10-mL venous blood sample was taken from each patient at baseline and the end of the intervention (day 5). Total complete blood count (CBC), hemoglobin (Hb) concentrations, and hematocrit (HCT) were measured by a cell counter. Erythrocyte sedimentation rate (ESR) was measured using the Wintergreen method. Also, serum was extracted from the whole blood using a centrifuge for 10 min at 3000 RPM, and then, serum concentrations of CRP were measured by the enzyme-linked immunosorbent assay (ELISA) method. Serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) were measured via the enzymatic colorimetric method using commercial kits (Pars Azmoon Inc, Tehran, Iran). The enzymatic method based on urease was used to measure BUN (Pars Azmoon Inc, Tehran, Iran). Serum creatinine (Cr) was determined using spectrophotometric assays (Pars Azmoon Inc, Tehran, Iran).

2.8. Statistical analysis

All statistical analyses were done using the SPSS software version 18 (SPSS, Inc. Chicago, IL, USA). The analyses were performed on the basis of a per-protocol (PP) approach. Therefore, we excluded patients with missing values or those who excluded during the trial. The Kolmogorov-Smirnov test was used to examine the normal distribution of quantitative variables. We normalized the non-normally distributed variables using log transformation. To detect differences in quantitative and categorical variables between the naproxen and placebo groups, we used the independent sample *t*-test and Chi-square test, respectively. Multivariate odds ratios (ORs) and 95% confidence intervals (CIs) for improvement in clinical symptoms of COVID-19 infection in the naproxen group, compared with the placebo group, were obtained using binary logistic regression by considering age, gender, and smoking as covariates. Furthermore, ORs and 95% CIs for the time to clinical improvement, defined by a seven-category ordinal scale, were calculated at the end of the trial (day 5) and days 7, 14, 21, and 28 of post-intervention in the naproxen group compared with the placebo group. Also, the hazard ratio (HR) along with 95% CI for death during the trial was obtained by the use of the Cox proportional-hazards model. To determine the effect of naproxen on laboratory parameters, respiratory rate, Sao_2, and blood pressure, the multivariate analysis of covariance (ANCOVA) was applied. In this analysis, mean changes that were adjusted for baseline measurements, age, gender, and smoking were obtained by considering end-of-intervention and baseline values. We also used the repeated-measures analysis of variance (ANOVA) to obtain the interaction between time and intervention groups. In this analysis, the intervention groups (naproxen compared with placebo) was considered as the between-subjects factor and the time points (five-time points for respiratory rate, Sao_2, and blood pressure and two-time points for laboratory parameters) were considered as the within-subjects factor. In all analyses, P-value<0.05 was considered as a significant level.

3. Results

Of the 80 patients who underwent randomization, two patients were excluded from the placebo group due to changes in medications (n = 1) and unwillingness to continue the trial (n = 1) and one patient was excluded from the naproxen group because the attending physician refused to prescribe naproxen after randomization. In total, 39 patients in the naproxen group and 38 patients in the placebo group completed the trial and were included in the statistical analysis. On average, all naproxen and placebo capsules were taken throughout the trial and therefore, the compliance to the intervention was 100%.

Baseline characteristics of patients in the naproxen and placebo groups are shown in Table 1. No significant difference was seen in terms of age, gender, marital status, smoking, and respiratory rate between the 2 groups. In addition, the distribution of patients with fever, diabetes, hypertension, cardiovascular diseases (CVDs), obesity, liver diseases, and kidney diseases was not statistically different between the 2 groups.

Clinical symptoms of COVID-19 infection from baseline to the fifth day of the intervention and OR (95% CI) of improvement at the fifth day, comparing the naproxen with the placebo group, are presented in Table 2. The prevalence of cough and shortness of breath decreased in the 2 groups throughout the trial; however, this improvement in the naproxen group was significantly higher than the placebo group; such that, the improvement of cough and shortness of breath in the naproxen group was 2.90 (95% CI: 1.10−7.66) and 2.82 (95% CI: 1.05−7.55) times more than the placebo group, respectively. The prevalence of other symptoms reduced in the 2 intervention groups during the trial; nevertheless, this reduction was not significantly different between the 2 groups.

Supplemental Figure 2 shows odds ratio and 95% CI for the time to clinical improvement, according to a seven-category ordinal

Table 1
Baseline characteristics of participants in the naproxen and placebo groups.

Variables	Placebo (n = 38)	Naproxen (n = 39)	P-value*
Age (year)	46.21 ± 15.25	48.33 ± 13.70	0.52
Female (%)	42.1	46.2	0.72
Married (%)	87.2	85.7	0.85
Smoker (%)	15.4	11.4	0.61
Fever (%)	75.0	61.5	0.21
Respiratory rate per min	21.82 ± 3.32	21.20 ± 3.17	0.41
Coexisting conditions			
Diabetes (%)	12.8	20.0	0.40
Hypertension (%)	7.7	11.4	0.58
CVDs (%)	10.3	14.3	0.59
Obesity (%)	0	2.9	0.28
Liver diseases (%)	0	5.7	0.13
Kidney diseases (%)	5.1	5.7	0.91

Data are presented as mean (SD) or percent.
Abbreviations: SD: standard deviation, CVD: cardiovascular diseases.
*Obtained from the independent sample *t*-test or Chi-squared test.

Table 2
Clinical symptoms of COVID-19 infection from baseline to the fifth day of the intervention and OR (95% CI) of improvement at the fifth day, comparing the naproxen with placebo group[a].

	Baseline	Day 2	Day 3	Day 4	Day 5	Improvement[b]	
						OR	95% CI
Fever (%)							
Control	71.8	15.4	12.8	2.6	2.6	1.00	
Naproxen	60.0	2.9	0	0	0	0.56	0.19–1.62
Cough (%)							
Control	61.5	46.2	38.5	28.2	20.5	1.00	
Naproxen	80.0	60.0	45.7	17.1	14.3	2.90	1.10–7.66
Shortness of breath (%)							
Control	46.2	25.6	17.9	17.9	15.4	1.00	
Naproxen	68.6	48.6	37.1	20.0	14.3	2.82	1.05–7.55
Fatigue (%)							
Control	25.6	20.5	12.8	5.1	2.6	1.00	
Naproxen	20.0	11.4	0	0	0	0.83	0.26–2.61
Headache (%)							
Control	56.4	30.8	12.8	7.7	5.1		
Naproxen	40.0	17.1	8.6	5.7	2.9	0.53	0.20–1.41
Myalgia (%)							
Control	51.3	17.9	10.3	7.7	7.7	1.00	
Naproxen	52.9	14.3	14.3	2.9	2.9	1.27	0.49–3.24
Olfactory disorder (%)							
Control	10.3	10.3	7.7	7.7	5.1	1.00	
Naproxen	11.4	5.7	5.7	2.9	2.9	2.42	0.31–15.76
Taste disorder (%)							
Control	20.5	10.3	7.7	2.6	2.6	1.00	
Naproxen	20.0	8.6	8.6	2.9	2.9	1.10	0.31–3.82
Night weats (%)							
Control	35.9	23.7	10.3	5.1	0	1.00	
Naproxen	28.6	14.3	5.7	2.9	2.9	0.60	0.21–1.71
Trembling (%)							
Control	25.6	10.3	0	0	0	1.00	
Naproxen	8.6	0	0	0	0	0.28	0.07–1.16
Chest pain (%)							
Control	33.3	15.4	10.3	5.1	2.6	1.00	
Naproxen	31.4	14.3	5.7	5.7	5.7	0.78	0.27–2.25

Abbreviations: OR: odds ratio, CI: confidence interval.
[a] Improvement was defined as the elimination of each symptom at the fifth day compared with baseline.
[b] Obtained from the binary logistic regression and adjusted for age, gender, and smoking.

scale, at the end of the trial (day 5) and days 7, 14, 21, and 28 of post-intervention, comparing the naproxen with placebo groups. Patients assigned to the naproxen group did not have a time to clinical improvement different from that of patients assigned to the placebo group. This was also the case when we controlled the analysis for age, gender, and smoking. In terms of death due to COVID-19 infection, we calculated the HR (95% CI) in the naproxen group compared with the placebo group (data not shown in tables or figures). There was no significant association between treatment with naproxen and death in patients with COVID-19 infection (HR: 0.49, 95% CI: 0.09–3.28).

Means and adjusted mean changes of respiratory rate, Sao_2, blood pressure, and laboratory parameters throughout the trial in the naproxen and placebo groups are illustrated in Tables 3 and 4. Mean changes in these variables were calculated by considering baseline and end-of-intervention values and by controlling for baseline measurements, age, gender, and smoking. Respiratory rate in the 2 groups decreased throughout the trial; but, this reduction was not significantly different between the naproxen and placebo groups. Also, treatment with naproxen had no significant effect on Sao_2 and diastolic blood pressure compared with placebo. However, we found a significant reduction in systolic blood pressure in the placebo group in comparison to the naproxen group (-5.59 ± 1.50 mmHg in the placebo group compared with -0.48 ± 1.59 mmHg in the naproxen group, $P = 0.02$). Also, a significant interaction was found between time and group in terms of systolic blood pressure ($P_{interaction} = 0.002$). Regarding laboratory parameters, treatment with naproxen had a significant increasing effect on mean corpuscular volume (MCV) when comparing to placebo (0.82 ± 0.47 fL in the naproxen group compared with -0.51 ± 0.47 fL in the placebo group). However, this effect was marginally significant ($P = 0.05$). Moreover, we found a significant interaction term between time and group for MCV ($P_{interaction} = 0.03$). For other laboratory parameters, naproxen administration revealed no significant effect.

3.1. Safety

One patient in the naproxen group and two patients in the placebo group reported gastrointestinal problems between baseline and the end of the trial. It should be noted that since these problems had occurred in the placebo group, other drugs prescribed in the routine treatment might be involved in the incidence of these problems.

4. Discussion

In total, treatment with naproxen could significantly improve cough and shortness of breath in patients with COVID-19 infection. In addition, naproxen administration resulted in a significant

Table 3
Means and adjusted mean changes of respiratory rate, Sao_2, and blood pressure throughout the trial in the naproxen and placebo groups.

	Baseline	Day 2	Day 3	Day 4	Day 5	P[b]	Mean change[a]	P[c]
Respiratory rate						0.45		0.62
Naproxen	21.20 ± 0.55	19.82 ± 0.48	19.97 ± 0.49	20.14 ± 0.34	20.14 ± 0.35		−1.37 ± 0.36	
Control	21.82 ± 0.52	20.82 ± 0.46	20.79 ± 0.47	20.35 ± 0.32	20.41 ± 0.33		−1.12 ± 0.34	
Sao_2						0.17		0.38
Naproxen	94.85 ± 0.63	96.60 ± 0.35	96.77 ± 0.42	96.45 ± 0.78	96.97 ± 0.80		1.52 ± 0.78	
Control	96.00 ± 0.59	96.66 ± 0.33	96.48 ± 0.40	95.92 ± 0.74	96.05 ± 0.75		0.57 ± 0.74	
SBP (mmHg)						0.002		0.02
Naproxen	110.94 ± 2.16	109.17 ± 1.61	113.02 ± 1.79	114.22 ± 1.59	112.94 ± 1.59		−0.48 ± 1.59	
Control	116.15 ± 2.05	110.51 ± 1.52	112.74 ± 1.70	108.20 ± 1.51	108.33 ± 1.51		−5.59 ± 1.50	
DBP (mmHg)						0.18		0.08
Naproxen	70.37 ± 1.38	67.77 ± 1.52	71.42 ± 1.41	70.97 ± 1.22	70.82 ± 1.45		−0.04 ± 1.48	
Control	71.66 ± 1.31	69.48 ± 1.44	71.28 ± 1.33	68.33 ± 1.15	67.59 ± 1.37		−3.63 ± 1.40	

Data are presented as mean ± SE.
Abbreviations: Sao_2: O2 saturation, SBP: systolic blood pressure, DBP: diastolic blood pressure.
[a] Mean changes were obtained by considering baseline and end-of-intervention values and adjusted for age, sex, smoking, and baseline measurements.
[b] P-value for time*group interaction: obtained from the repeated measure ANOVA.
[c] P-values for difference between mean changes: obtained from the analysis of co-covariance (ANCOVA).

Table 4
Mean of laboratory parameters at different times of intervention in the naproxen and placebo groups as well as their mean changes during the intervention period.

	Baseline	Day 5	P	Adjusted change	P
BUN			0.44		0.75
Naproxen	21.04 ± 3.46	18.83 ± 3.31		1.00 ± 3.40	
Control	12.24 ± 3.39	14.80 ± 3.24		−0.52 ± 3.33	
Creatinine			0.70		0.69
Naproxen	1.01 ± 0.06	1.04 ± 0.14		0.02 ± 0.13	
Control	1.03 ± 0.06	1.13 ± 0.13		0.10 ± 0.13	
AST			0.58		0.53
Naproxen	42.94 ± 6.91	31.00 ± 3.30		−7.80 ± 3.05	
Control	34.57 ± 6.73	27.94 ± 3.21		−10.55 ± 2.97	
ALT			0.68		0.32
Naproxen	37.50 ± 5.60	28.05 ± 3.94		−8.52 ± 3.05	
Control	35.42 ± 5.45	23.47 ± 3.84		−12.81 ± 2.97	
ALP			0.20		0.83
Naproxen	217.88 ± 18.57	191.88 ± 14.20		−16.18 ± 9.08	
Control	179.15 ± 18.08	174.94 ± 13.82		−13.50 ± 8.82	
CRP			0.97		0.97
Naproxen	2.00 ± 0.29	1.88 ± 0.28		−0.10 ± 0.24	
Control	1.65 ± 0.27	1.55 ± 0.26		−0.11 ± 0.23	
ESR			0.60		0.86
Naproxen	49.83 ± 5.99	56.38 ± 6.63		9.18 ± 5.40	
Control	27.00 ± 5.68	37.20 ± 6.29		7.83 ± 5.08	
WBC			0.60		0.96
Naproxen	7.09 ± 0.59	7.20 ± 0.66		0.29 ± 0.54	
Control	6.54 ± 0.57	7.06 ± 0.64		0.33 ± 0.53	
RBC			0.77		0.97
Naproxen	4.75 ± 0.17	4.47 ± 0.18		−0.30 ± 0.11	
Control	5.05 ± 0.16	4.73 ± 0.17		−0.29 ± 0.10	
Hb			0.51		0.90
Naproxen	12.55 ± 0.43	11.96 ± 0.45		−0.71 ± 0.30	
Control	13.73 ± 0.42	12.86 ± 0.45		−0.76 ± 0.30	
HCT			0.28		0.93
Naproxen	38.21 ± 1.17	36.34 ± 1.17		−2.47 ± 0.84	
Control	42.10 ± 1.15	38.96 ± 1.14		−2.56 ± 0.82	
MCV (fL)			0.03		0.05
Naproxen	83.20 ± 1.63	84.12 ± 1.61		0.82 ± 0.47	
Control	83.71 ± 1.63	83.11 ± 1.61		−0.51 ± 0.47	
MCH			0.28		0.47
Naproxen	26.85 ± 0.67	27.09 ± 0.60		0.18 ± 0.14	
Control	27.38 ± 0.68	27.34 ± 0.62		0.02 ± 0.15	
PLT			0.51		0.29
Naproxen	221.45 ± 13.54	262.37 ± 18.16		45.92 ± 17.76	
Control	205.52 ± 13.26	229.20 ± 17.80		18.87 ± 17.39	
Lymphocytes			0.55		0.57
Naproxen	3.97 ± 1.69	5.06 ± 1.97		1.08 ± 0.92	
Control	6.16 ± 1.59	6.50 ± 1.85		0.35 ± 0.87	
PMN			0.80		0.82
Naproxen	16.72 ± 5.73	15.23 ± 5.17		−1.42 ± 1.24	
Control	19.80 ± 5.62	18.81 ± 5.06		−1.03 ± 1.21	

Data are presented as mean ± SE.
Abbreviations: BUN: blood urea nitrogen, SGOT: serum glutamic oxaloacetic transaminase, SGPT: serum glutamic pyruvic transaminase, ALP: alkaline phosphatase, CRP: C-reactive protein, ESR: rythrocyte sedimentation rate, WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, HCT: hematocrit, MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, PLT: platelet, PMN: polymorphonuclear neutrophils.
[a] Mean changes were obtained by considering baseline and end-of-intervention values and adjusted for age, sex, smoking, and baseline measurements.
*P-value for time*group interaction: obtained from the repeated measure ANOVA.
**P-values for difference between mean changes: obtained from the analysis of covariance (ANCOVA).

increase in MCV. Furthermore, naproxen had a preventive effect on the reduction of systolic blood pressure in COVID-19 patients. For other COVID-19-related symptoms and laboratory parameters, we found no significant effect following naproxen administration. To the best of our knowledge, this clinical trial is the first to examine the effect of naproxen intake on COVID-19 infection.

Coronavirus disease is a viral infection that is spreading rapidly all over the world [16]. Many researchers are trying to find an effective protocol for the prevention and treatment of this infection. However, until now, many proposed protocols and therapeutic methods have not achieved this goal. Therefore, the main purpose of the current therapeutic approaches is to control the symptoms and life-threatening complications of COVID-19 infection. Many medications including NSAIDs have been proposed for the management of COVID-19 symptoms [17]. Amongst NSAIDs, ibuprofen, diclofenac, aspirin, and indomethacin are commonly prescribed for this purpose [17]. However, using naproxen, as a known NSAID, has been a question for researchers and clinicians. No study has examined the efficacy of this drug in COVID-19 patients. In the current study, we found that treatment with naproxen improved cough and shortness of breath in COVID-19-infected patients. In line with our findings, Sperbert et al. reported that oral administration of naproxen for five days could alleviate cold symptoms, compared to placebo, among Rhinovirus-infected patients but the viral titers and serum antibody responses were not different between the 2 groups [12]. In the study of Gwaltney et al., treatment with a combination of intranasal interferon-alpha 2b and ipratropium and oral naproxen for four days could improve rhinorrhea, cough, malaise, nasal obstruction, and sore throat and overall mean total symptom scores [18]. Also, viral shedding time and virus titer in the treated group were lower than the control group. In another study, influenza patients with clarithromycin-naproxen-oseltamivir combination therapy experienced a shorter period of disease and a more rapid decline of influenza virus titer than the oseltamivir-treated group [19]. Overall, it seems that treatment with naproxen can be an option for the management of symptoms in influenza-like diseases. However, further studies are needed to confirm this issue among COVID-19-infected patients.

It must be kept in mind that naproxen not only had positive effects in controlling cold symptoms but also did not cause serious side effects. Some NSAIDs cause gastrointestinal side effects including nausea, vomiting, indigestion, diarrhea, and even gastric ulceration or bleeding [20]. However, in the current study, we found that naproxen had no serious side effects. The safety of naproxen has been confirmed in previous studies [21]. In a systematic review on clinical trials administrating NSAIDs, Yousefifard et al. concluded that naproxen is one of the safest types of NSAIDs for patients with severe influenza [21]. However, further assessments are required in this regard.

It has been shown that naproxen exerts antiviral activity against some types of influenza viruses by inhibiting nucleoprotein (NP) binding to RNA [10]. However, the antiviral effect on the COVID-19 virus is not clear. Unfortunately, in the current study, we could not assess the viral titers and serum antibody responses to determine this effect. In addition to the antiviral activities, naproxen has anti-inflammatory properties through inhibiting cyclooxygenase (COX) and consequently, the reduced production of inflammatory mediators such as prostaglandins [22]. Therefore, the beneficial effects of naproxen on cough and shortness of breath in COVID-19 patients might be explained by the possible antiviral and also anti-inflammatory properties of this drug. However, further studies are needed to shed light facts on this regard.

In the current study, we found that naproxen resulted in increased MCV COVID-19 patients compared to placebo. The effect of naproxen on MCV was also reported in an experimental study in

which both red cell mass and MCV increased in naproxen-treated rats [23]. Moreover, we observed that treatment had a preventive effect on the reduction of systolic blood pressure in COVID-19 patients. This effect might be justified by the increasing effect of naproxen on systolic blood pressure shown in previous studies [24]. Naproxen decreases the production of prostaglandin I_2 through its inhibitory effects on cyclooxygenase (COX) enzyme [25]. Prostaglandin I_2 has a role in vasodilatation and preventing the proliferation of vascular smooth-muscle cells [25].

Some limitations should be considered when interpreting our findings. Because of limited financial resources, we could not examine the effect of naproxen intake on virologic measures including viral titers and viral RNA load. Although there was no difference between the naproxen and placebo group in terms of age, gender, and smoking, differences in other factors related to COVID-19 infection such as disease severity at baseline might affect our results. However, in the present study, some indicators of disease severity such as fever, Sao_2, and respiratory rate were not significantly different between the 2 groups. We assessed a single dose of naproxen on COVID-19 infection and therefore, determine the most effective dose of naproxen in the current study is impossible. Due to the low sample size, we could not perform stratified analysis based on gender, smoking, and other important variables.

5. Conclusion

In conclusion, treatment with naproxen improved cough and shortness of breath in patients with COVID-19 infection. However, we found no significant effect on other symptoms. Also, naproxen administration resulted in a significant increase in MCV and had a preventive effect on the reduction of systolic blood pressure in COVID-19 patients. Further studies are needed to determine the definite dose of naproxen and to examine the effect of this drug on virologic measures of COVID-19 infection.

Authors' contribution

SS, ER, SM, SJ, ME, AM and SA: contributed to the conception, design, and data collection; SM, SB, FZ, and AC: contributed to the sampling, data gathering, and laboratory assessments. SN, MA and SM: contributed to the statistical analysis and drafting of the manuscript; and SM: supervised the study. All authors read and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare that they have not any conflict of interest about this work.

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Noun.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2021.102319.

Data availability statement

The data generated or analyzed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

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