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Evaluation of Anti-inflammatory Effects of Naproxen on Pro-inflammatory Cytokines in COVID-19 Patients

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ABSTRACT

Background:COVID-19 (coronavirus disease 2019) was declared as a pandemic by the World Health Organization (WHO) in early 2020. The spectrum of clinical symptoms of COVID-19 patients, including asymptomatic and symptomatic cases, includes dry cough, fatigue, fever, shortness of breath, and gastrointestinal symptoms. However, increased immune inflammatory responses to stimuli could result in overproduction of pro-inflammatory cytokines, immunopathological complications, and death in patients with COVID-19. Given the anti-inflammatory effects of naproxen, this study aimed to evaluate the effect of naproxen on IL-1β, TNF-α, IL-6, IFN-γ, and TGF-β in COVID-19 patients.

Materials & Methods: Serum levels of IL-1β, TNF-α, IL-6, IFN-γ, and TGF-β were determined by a commercial ELISA (enzyme linked immunosorbent assay) kit before and after naproxen treatment.

Findings: According to the results, serum levels of IFN-γ and TGF-β cytokines significantly decreased in patients after treatment with naproxen. In addition, naproxen treatment was effective in reducing the serum levels of IL-6 and IL-1β in patients with COVID-19; however, it did not significantly change the serum level of TNF-α.

Conclusion: Overall, the findings demonstrated the effectiveness of naproxen on regulating the serum levels of pro-inflammatory cytokines in COVID-19 patients.

Keywords: Naproxen, inflammatory cytokines, COVID-19

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Introduction

Many cases of pneumonia of unknown causes were reported in Wuhan, China in December 2019, which spread quickly in different parts of the world [1, 2]. In its early stages, the disease was observed as an acute respiratory infection which progressed rapidly to an acute respiratory distress syndrome (ARDS), leading to complex problems in some patients [2, 3]. However, it did not take long to find out that a new coronavirus named new coronavirus 2019 (nCoV-2019) was the cause of the disease (called COVID-19) in January 2020 [4]. The World Health Organization (WHO) reported the new coronavirus in Wuhan as an international public health emergency [2, 4, 5]. Coronaviruses could mainly cause respiratory infections in humans [6]; two highly pathogenic of which leading to epidemics in recent years include severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Similar to SARS and MERS, nCoV-2019 has a zoonotic origin, although it is transmitted directly between two individuals via body secretions [2-4]. The incubation period of the disease is between 2-14 days with symptoms like dry cough, fever, fatigue, shortness of breath, and gastrointestinal complications [6, 7]. Many patients with COVID-19 do not demonstrate acute symptoms and have a good prognosis; however, in a small number of patients (up to 20%), the disease is associated with severe pneumonia, pulmonary edema, multiple organ failure, and eventually death [3, 4, 8, 9].

Complications and mortality of viral respiratory infections are mostly attributable to overproduction of pro-inflammatory cytokines and host inflammatory responses, resulting in immunopathological complications [2, 10, 11]. The pathogenesis of COVID-19 is, in turn, caused by the infiltration of immune cells into the lungs, leading to severe lung damage and rapid spread of the virus to other organs, followed by overproduction and systemic production of inflammatory cytokines and inflammatory chemokines. Innate immune responses are considered as the front line of defense against viral infections in the body [4-6]. However, increased immune responses to the infection could lead to severe inflammatory responses, immunopathological complications, and COVID-19 pathogenesis in patients [6, 7].

Elevated pro-inflammatory cytokines such as interleukin-1 levels could give rise to acute inflammatory responses and tissue damage, which eventually cause cytokine storm, immunopathological complications, and death [2, 12]. Cytokines produced by Th1 cells, like IFN-γ, TNF-α, TNF-β, and IL-2, play a major role in antiviral immunity by inducing CD8 T cells, stimulating NK cells, and regulating cellular immunity [5, 7]. In turn, cytokines produced by Th2 cells, such as IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13, mediate humoral immune responses and antibody production. An imbalance between cytokines and Th1/Th2 chemokines could however lead to pathological changes and insufficient recovery in patients [1, 4, 11]. High serum levels of IFN-γ, IL-1, IL-6, IL-12, and TGF-β have been reported in patients with acute form of SARS [8]. Compared to the moderate form of the disease, elevated serum levels of pro-inflammatory cytokines IL-6 and IFN-α and chemokine IL-8 have also been reported in patients with severe MERS [4, 7]. High serum levels of such cytokines are deemed to be attributable to their role in lung pathology and the disease immunopathogenesis in humans [8, 9, 12]. In addition to antiviral drugs approved for COVID-19 treatment, including nirmatrelvir-ritonavir (Paxlovid), remdesivir (Veklury), or molnupiravir (Lagevrio), the main disease management strategies for COVID-19 include maintaining vital signs, partial arterial oxygen pressure, and

water and electrolyte balance, controlling blood pressure, and preventing secondary infections and organ failure in patients [2-4, 9]. The use of anti-inflammatory treatments is thus deemed to be beneficial in COVID-19 management [8, 12].

As a nonsteroidal anti-inflammatory drug (NSAID), naproxen blocks arachidonate binding to competitively inhibit both cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, which results in anti-inflammatory and immunomodulatory effects [11, 13, 14]. Some studies have reported the antiviral function of naproxen against influenza A and B viruses by interfering with the RNA replication process, which eventually inhibits influenza virus replication [14-17]. The concomitant use of a cyclooxygenase inhibitor with antiviral drugs has also been reported to significantly increase the survival of mice with H1N1 compared to mice receiving only antiviral drugs. In effect, naproxen as a NSAID prevents weight loss and pulmonary hemorrhage in influenza-infected mice [16, 18-20]. Likewise, the use of a combination of antibiotics (macrolides) and antivirals (oseltamivir) reduces some clinical signs, although they could not alter inflammatory cytokine levels, indicating that they could not be solely effective in reducing disease mortality [18, 21]. However, the concomitant use of macrolide antibiotics (clarithromycin), antivirals (oseltamivir), and naproxen has been demonstrated to significantly reduce mortality in patients with viral respiratory infections [18, 22]. This could probably be attributed to the negative regulation of severe inflammatory responses and the subsequent reduction in the production of proinflammatory cytokines [19, 22]. Therefore, naproxen could be taken as a safe, potent, and widely available drug in the case of pandemics of respiratory infections such as the COVID-19 pandemic or for cases resistant to antiviral drugs [23, 24].

Objectives: This paper aimed to examine the effects of naproxen on IL-1β, TNF-α, IL-6, IFN-γ, and TGF-β in patients with COVID-19.

Materials and Methods

Patients and study design: A total of 90 hospitalized patients in the acute phase of COVID-19, whose disease was confirmed based on clinical signs and laboratory tests (positive nasopharyngeal swab polymerase chain reaction for COVID-19), were recruited. A demographic questionnaire including patient age, sex, place of residence, underlying diseases, smoking status, and medication was filled by each patient. Based on the questionnaire results, 56% of the patients were male, and44% were female with an age range of 18 to 53 years, their common symptoms included fever, dry cough, fatigue, muscle weakness, and chest pain. Exclusion criteria were: admission to intensive care unit (ICU) prior to randomization, comorbidities, history of smoking, and pregnancy. After obtaining the approval of the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, the study was carried out in compliance with the Declaration of Helsinki. Verbal informed consent was obtained from all participants due to ethical considerations. Two blood samples were then collected from the patients: before naproxen treatment (250 mg twice daily for 5 days) and after naproxen treatment.

Measurement of cytokine levels: Before and after naproxen treatment, serum samples were obtained from patients' venous blood through centrifugation at 1500 rpm for 15 min and kept at −20 °C until analysis. Serum levels of IL-1β, TNF-α, IL-6, IFN-γ, and TGF-β were determined by a commercial ELISA (enzyme linked immunosorbent assay) kit according to the manufacturer's protocol (Karmania Pars Gene, Kerman, Iran). The lowest detection limit of IL-1β, TNF-α, IL-6,

IFN-γ, and TGF-β was 2, 2, 3, 3, and 6 pg/mL, respectively. The level of absorption was determined using an ELISA reader (BioTek; Winooski, Vermont, USA) at 450 nm.

Statistical analysis: Data analysis was done in GraphPad Prism 8.0, and differences between the two groups (e.g., before and after naproxen treatment) were valuated using Wilcoxon matched-pairs signed-rank test. The values were reported as mean ± standard deviation (SD), and the significance level was represented as $*p < .05$ and $**p < .01$.

Findings

Detection of pro-inflammatory cytokine profile by ELISA: To check the changes in cytokine levels before and after naproxen treatment, serum levels of IL-1β, TNF-α, IL-6, IFN-γ, and TGF-β cytokines were measured in the serum samples by ELISA. Table 1 lists serum levels of pro-inflammatory cytokines before and after naproxen treatment. The comparison between the mean serum levels of pro-inflammatory cytokines before and after naproxen treatment is also shown in Figure 1.

Effect of naproxen on IL-1β serum level: Based on ELISA findings (Figure 2), the serum level of IL-1β in COVID-19 patients decreased after treatment with naproxen, although the difference observed before and after treatment was not significant ($p> .05$).

Effect of naproxen on TNF-α serum level: As shown in Figure 3, there was no significant difference between serum levels of TNF-α before and after NSAID treatment ($p> .05$).

Effect of naproxen on IL-6 serum level: According to the obtained results (Figure 4), naproxen treatment reduced the serum level of IL-6 in COVID-19 patients, although the difference between the two groups was insignificant ($p> .05$).

Effect of naproxen on IFN-γ serum level:

Table 1) Serum levels of pro-inflammatory cytokines before and after naproxen treatment

	IL-1β		TNF-α		IL-6		IFN-γ		TGFβ	
	Before	After	Before	After	Before	After	Before	After	Before	After
Mean	11.55	9.958	10.61	26.41	8.843	6.888	62.93	52.12	53.73	40.68
Std. deviation	27.35	29.69	31.48	89.87	7.765	6.032	26.87	18.78	42.9	62.11
Std. error of the mean	4.078	4.426	4.692	13.4	1.158	0.8992	4.006	2.799	6.396	9.259
P value	.3018		.3094		.0548		.0147		.0031	

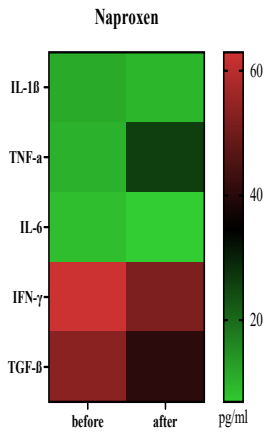

Figure 1) Changes in the mean serum levels of the relevant cytokines before and after naproxen treatment.

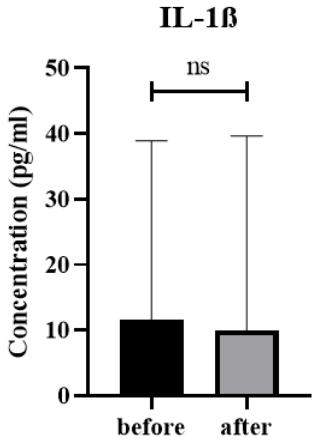

Figure 2) The serum level of IL-1β in the paitients with COVID-19 before and after Naproxen treatment. Significance was presented as $*p<0.05$, $**p<0.01$

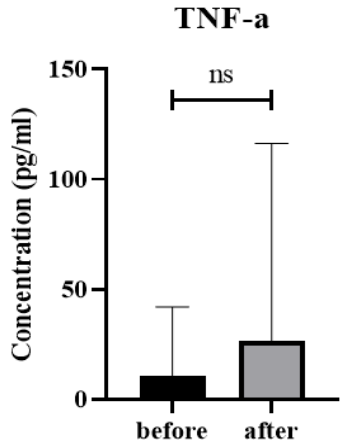

Figure 3) The serum level of TNF-α in the paitients with COVID-19 before and after Naproxen treatment. Significance was presented as *p<0.05, **p<0.01

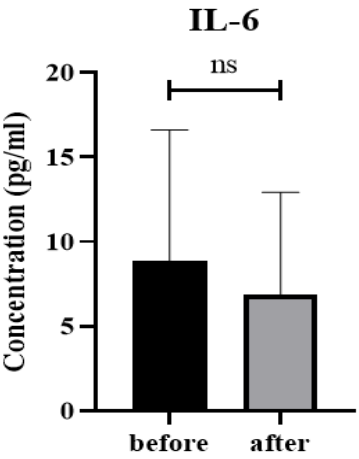

Figure 4) The serum level of IL-6 in the paitients with COVID-19 before and after Naproxen treatment. Significance was presented as *p<0.05, **p<0.01

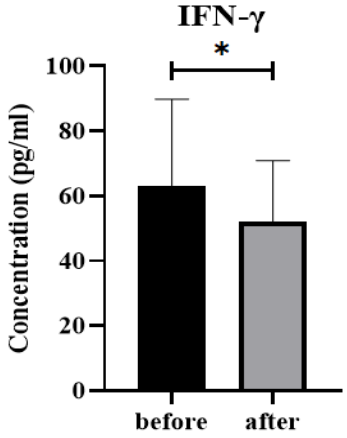

Figure 5) The serum level of IFN-γ in the paitients with COVID-19 before and after Naproxen treatment. Significance was presented as *p<0.05, **p<0.01

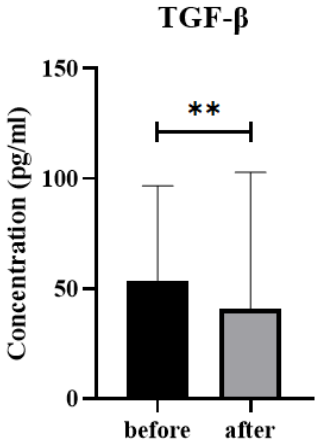

Figure 6) The serum level of TGF-β in the paitients with COVID-19 before and after Naproxen treatment. Significance was presented as *p<0.05, **p<0.01

As shown in Figure 5, the serum level of IFN-γ in COVID-19 patients significantly decreased after naproxen treatment (p< .05).

Effect of naproxen on TGF-β serum level: According to the results, the serum level of TGF-β decreased significantly after the treatment of patients with naproxen compared to the pretreatment values (p< .01) (Figure 6).

Discussion

The immunopathology and pathogenesis of MERS and SARS are strongly associated with the expression level of inflammatory cytokines. This is because even with suppressive antiviral therapy, pro-inflammatory cytokines continue to drive immunopathologic progression with viral replication [25-29]. High serum levels of pro-inflammatory cytokines, including IL-1β, IL-6, IFN-γ, and TNF-a, have been reported in severe COVID-19 cases. The findings indicate that naproxen treatment has some anti-inflammatory effects on inflammatory cytokines in COVID-19 patients. In turn, neutrophils, macrophages, and Th1 and Th17 cells are responsible for antiviral activity and inflammatory responses [30, 31]. According to recent studies, T cells cause a cytokine storm by overproduction of inflammatory cytokines such as IL-1β, IL-6, TNF-α, and

IFN-γ. A correlation has also been reported between the severity of COVID-19 and the levels of Th17 cells and their cytokines such as IL-1β, IL-6, IFN-γ, and TNF-α. Moreover, depletion of Treg cells and their relevant cytokines such as TGF-β and IL-10 as well as imbalanced Th17/Treg cell ratios possibly increase inflammatory responses and the disease pathogenesis in COVID-19 patients [2, 32]. In addition, there is an association between IL-1β and neutrophil infiltration, tissue damage, acute inflammatory responses, higher case fatality, and severe respiratory viral infections in patients [33-35]. Moreover, higher levels of IL-1β have been reported in patients with COVID-19 [30, 32, 35]; however, the present study results indicated that IL-1β levels decreased in patients after naproxen treatment.

TNF-a, as another potent pro-inflammatory cytokine, is an important antiviral cytokine. Studies have reported high levels of TNF-α in *in vitro* studies of SARS and MERS [36-38]. Studies have also indicated that elevated levels of TNFα, IL-6, and IL-1β are related to ARDS in COVID-19 patients [29, 39]. Besides, cytokine storm is observed in severe COVID-19 patients due to increased inflammatory cytokines like TNF-α and IL-6 [29, 37, 39]. The present study results showed that TNF-α level did not significantly increase in patients after treatment with naproxen. IL-6 is a key mediator of the host response following tissue injury, infection, and inflammation [40]. Some studies have shown a significant association between IL-6, TNF-α, and CRP (C-reactive protein) and the disease severity [41]. On the contrary, some other studies have reported that there is no significant difference in TNF-α, IL-6, and IL-1β levels between severe and non-severe cases based on inflammatory profiles measured prior to the onset of cytokine storm [40, 42]. The present study findings also showed that naproxen reduced the serum IL-6 levels in COVID-19 patients, although its effects were statistically insignificant. This could be due to different factors such as variability in patients and cytokine levels assayed by ELISA.

IFN-γ, as a potent cytokine with strong inflammatory properties and antiviral activity, has a considerable correlation with viral load, indicating that the virus could increase the secretion of these cytokines [36, 39]. Mononuclear cells, including T cells, are the top sources of IFN–γ [26, 28, 30]. Recent studies have highlighted that IFN-γ and IL-6 levels are higher in patients suffering from a severe type of COVID-19 compared with those suffering from a moderate type [29, 39, 43]. On the other hand, studies have highlighted that low circulation of IFN-γ is a risk factor of lung fibrosis in COVID-19 patients [37, 44]. In addition, the protective role of IFN-γ in kidney fibrosis has been recognized. However, some studies have reported no significant difference between moderate and severe COVID-19 in terms of IFN-γ levels [36, 44]. Based on the results, naproxen reduced the serum levels of IFN-γ and showed anti-inflammatory effects in COVID-19 patients. However, the downregulation of IFNs and the control of the pro-inflammatory cytokine storm in COVID-19 patients is still unknown [38, 39]. Likewise, TGF-β acts as a major mediator of acute lung injury, and its pathway is the main target for anti-fibrotic therapies [29, 37]. The migration of inflammatory cells into the lungs could explain the local increase of TGF-β in the late and severe phases of COVID-19 infection [36, 40, 41]. It has been reported that TNF-α could upregulate TGF-β in respiratory viral infections such as COVID-19 [37, 38]. Some studies have indicated that the relationship between IFN-γ and TGF-β contributes to the evolution of COVID-19, given that respiratory distress and lung fibrosis are mainly due to cytokine storm and TGF-β overproduction [2, 30, 36, 38]. The results of this study showed

that the serum level of TGF-β significantly decreased after naproxen treatment in COVID-19 patients.

Recent studies have likewise highlighted the correlation between COVID-19 severity and Th17 cell levels and their cytokines such as IL-1β, IL-6, IFN-γ, and TNF-α [30, 31, 34]. Also , depletion of Treg cells and their relevant cytokines such as TGF-β and IL-10 and imbalanced Th17/Treg cell ratios possibly contribute to higher inflammatory responses and the disease pathogenesis in COVID-19 patients [37, 38, 42].

Regarding limitations, it is notable that the sample size used in the present work was relatively small, including 90 patients with COVID-19. Moreover, the lack of statistical significance is likely attributable to factors such as variability in patients and cytokine levels determined by ELISA. In addition, it was not possible to screen for other respiratory pathogens and other changes in pro-inflammatory cytokine profiles in COVID-19 patients.

Conclusion

In conclusion, naproxen treatment could be effective in the management of COVID-19 by regulating serum levels of pro-inflammatory cytokines in patients. More studies are needed to evaluate the effectiveness of NSAIDs, including naproxen as an immunomodulating drug, in the control of symptoms associated with cytokine storm and the management of COVID-19.

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Authors' contributions: Arshid Yousefi Avarvand, Farhad Abolnezhadian, and Manoochehr Makvandi conceived and designed this research. Arshid Yousefi Avarvand, Azar Dokht Khosravi, Manoochehr Makvandi, and Sara Iranparast conducted experiments. Mehran Varnaseri, Seyed Ahmad Alavi, and Gholamreza Shariati analyzed the data. Arshid Yousefi Avarvand and Farhad Abolnezhadian wrote the manuscript. All authors read and approved the manuscript.

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