Original Research Article

THE ROLE OF NIMESULIDE IN THE TREATMENT OF COVID-19 INFECTION

ABSTARCT

Objective:

There are different anti-inflammatory drugs that are being used in patients with moderate to severe COVID-19 infection. However, in mild to moderate COVID-19 infection, Nimesulide treatment might impede the inflammation with a superior safety profile. Therefore, this study is intended to assess the anti-inflammatory, analgesic and antipyretic activity of Nimesulide in mild to moderate Covid-19 infection.

Methodology:

This was an uncontrolled longitudinal study conducted at Pakistan Institute of Medical Sciences Islamabad. The duration of the study was about six months. A total of 66 patients were enrolled. All the patients received Nimesulide 100 mg along with 10 ml sucralfate suspension two times a day for five days. Patients with elevated C-reactive protein or further comorbidities were prescribed 250 mg azithromycin two times a day for five days. Patients with elevated D-dimer (above 500) or other comorbidities were prescribed enoxaparin in a dose of 60 mg subcutaneously once daily for five days. The Primary outcome was estimated in terms of a percent change in oxygen saturation, hospitalization, or death.

Results:

The results showed that 31(47.0%) were females and 35(53.0%) were males. The mean oxygen saturation on presentation was 93%±7.9. 24(36.36%) of the patients had D-dimer levels < 250 ng/ml, while 30(45.45%) of the patients had D-dimer levels >250 ng/ml with significant difference between them (p=0.025). 16(24.24%) patients received enoxaparin while 49(74.24%) patients did not received enoxaparin and found a significant difference between the mean change

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in oxygen saturation of them ($p<0.001$). 47(71.2%) patients received azithromycin while 19(28.8%) patients did not received azithromycin and found a significant difference between the mean change in oxygen saturation of them ($p=0.03$).

Conclusion:

This study concluded that Nimesulide treatment resulted in a rapid temperature fall within five days. Furthermore, oxygen saturation was also significantly improved in patients treated with Nimesulide.

Keywords: Nimesulide, mild to moderate Covid-19 infection, azithromycin, enoxaparin

INTRODUCTION

COVID-19 is a serious public health concern worldwide. However, the use of different Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) have not been studied so far in COVID-19 patients other than Ibuprofen [1]. COVID-19 presents in different phases of infection severity ranging from mild, moderate, to severe [2]. Even when mild/asymptomatic patients are managed at home with self-medication, moderately ill patients require hospitalization, whereas severely infected COVID-19 patients require intensive care [3]. COVID-19 critical care remains inconsistent because there is such a variety of comorbid conditions and complications among the critically ill and the rapid nature of the disease [4].

A lot of clinical research is being conducted; most, including the antiviral and antimalarial medicines, such as lopinavir/ritonavir and chloroquine (CQ) or hydroxychloroquine (HCQ), have shown antiviral activity against SARS-CoV-2 in vitro [5]. Accordingly, it is predicted that immunomodulatory drugs may be helpful in managing COVID-19 infections because SARS coronaviruses are known to cause inflammation and lung damage in moderate-to-severe infections [6].

In contrast, Nimesulide (N-[4-nitro-2-phenoxyphenyl]-methane sulfonamide) is a therapeutically effective Non-Steroidal Anti-Inflammatory Drug (NSAID) [7]. Generally, this class of medicines has been used due to its anti-inflammatory, analgesic, and antipyretic properties [8]. NSAIDs commonly cause liver toxicity, which has been linked to their uncoupling effects on

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mitochondria [9]. Due to the risk of hepatotoxicity, Nimesulide, though currently made available, was previously banned on the market in many nations in the past, such as Belgium, Spain, Finland, the United States, and Ireland [10].

NSAIDs are associated with an increased risk of adverse effects, particularly in acute viral respiratory infections as well as COVID-19 disease [11]. Hence, it is important to discover drugs with significant immunomodulatory properties. Azithromycin (AZM), an antibacterial macrolide, has a unique and remarkable position in this regard for treatment of COVID-19 infections. It has been confirmed that AZM has significant antiviral properties. Researchers have demonstrated that it has antiviral effects against a large group of viruses, including Respiratory Syncytial Virus, Ebola, Zika, Influenzae H1N1 Virus, Rhinovirus, and Enterovirus [12-16]. In a randomized trial in newborn babies, its antiviral properties were demonstrated against respiratory syncytial virus [17]. Combining Azithromycin with HCQ exhibited synergistic antiviral activity against SARS-CoV-2 both in vivo and in vitro [18, 19]. Besides its pharmacological properties, Azithromycin also has an intriguing therapeutic role in the treatment of COVID-19. A high average concentration of this substance has been found in both intracellular and extracellular fluids of lung tissues [20].

Complications of COVID-19 infections include coagulopathies [21], mostly in critical situations of infection [22]. COVID-19 infections were determined by one study by looking at hematological factors [23]. Researchers are comparing anticoagulation treatments, though due to the widespread occurrence and severe infection, it is important to assess observational data to create proof to direct treatment [24]. As part of the management of COVID-19 patients, several anticoagulants are being administered, such as Enoxaparin, unfractionated heparin, and Rivaroxaban [25]. A study reported that the standardized dosage of Enoxaparin enhances survival rates and reduces hospitalizations in advanced age of > 50 years in symptomatic ambulatory cases [26].

Internationally, various studies have been conducted to determine the treatment for Covid 19 infection, but it remains a matter of debate. Thus, the purpose of this study is to assess the effects of Nimesulide on patients with Covid-19.

METHODOLOGY

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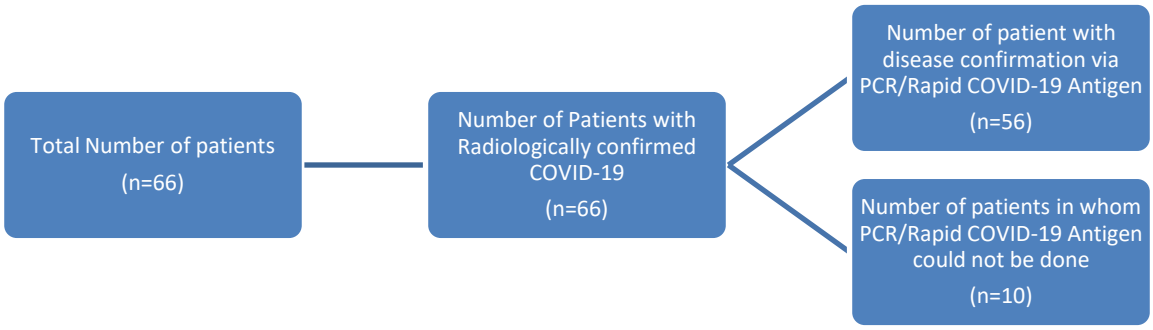
We used a purposive sampling technique to conduct this uncontrolled longitudinal study at Pakistan Institute of Medical Sciences Islamabad. The study lasted about six months from August 2020 till February 2021. After obtaining ethical approval from the ethical Review Board (ERB) of Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad, (No. F.1-1/2015/ERB/SZABMU/605 Dated: 22nd July 2020), 66 patients were enrolled in this study. Patients vising the Emergency Department, Out-Patient Department or Rapid Access Clinic at the hospital were enrolled based on the inclusion and exclusion criteria. Informed written consent was signed by all the patient enrolled in this study.

A study population of adults aged 18 and over who had not previously been diagnosed or treated for infection with COVID-19 was included in the analysis. Patients with sensitivity to any study group, patients with contraindications to any of the study medications, active bleeding, having a history of myocardial infarction, peptic ulcer disease, taking an NSAID or Nimesulide, or unable to follow up were excluded from the study.

Nimesulide 100 mg was administered to all patients twice daily for five days, along with 10ml of sucralfate suspension twice daily for five days. Patients with elevated C-reactive protein or other comorbidities were given 250 mg azithromycin twice a day for five days. Enoxaparin was administered once a day for five days to patients with elevated D-dimer tests (over 500) or other comorbidities.

The baseline spO2 of all patients was measured and chest X-rays were repeated after five days. Primary outcomes were estimated as a percent change in oxygen saturation. Secondary outcomes included changes in oxygen saturation in patients needing Azithromycin and/or Enoxaparin, symptomatic improvement in fever following initiation of treatment and any adverse reactions reported by patients.



The data were entered and analyzed using SPSS version 22. We presented continuous variables such as age, TLC, D-dimer, and CRP as means, while categorical variables such as gender, other comorbidities, and radiological findings were presented as percentages and frequencies. A Chi-square test and T-test were used to assess the significance. A P value <0.05 was considered significant.

RESULT

A total of 66 patients were selected for the study, wherein 31(47.0%) of the study patients were females and 35(53.0%) were males. The mean age of the patients was 52.4±1.4 years. 28(42.42%) of the studied patients were hypertensive and 22(33.33%) had diabetes. On chest radiographic findings, all 66(100%) patients included had bilateral consolidations suggestive of COVID-19 infection. COVID PCR or COVID Rapid Antigen was positive in 56(84.0%) of the patients. 10 of the patients amongst the 66 included could not do a PCR or Rapid COVID-19 Antigen test but their radiological findings were suggestive of COVID-19 infection. The mean oxygen saturation on presentation was 93%±7.9. 28(42.42%) of the patients had CRP levels < 5.0 mg/L, while 30(45.45%) of the patients had CRP levels > 5.0 mg/L, with an insignificant difference between them (p=0.78). In 8 of the patients, CRP could not be done. 24(36.36%) of the patients had D-dimer levels < 250 ng/ml, while 30(45.45%) of the patients had D-dimer

levels > 250 ng/ml with significant difference between them (p=0.025). In 12 patient the D-dimers could not be done. Mean TLC count was found 7825±3370 /microliter. 32 (48.5%) patients used to wear mask while 36(54.5%) patients used sanitizer. The mean baseline oxygen saturation in patients who used sanitizer was 94.7±4.7 compared to 90.87±10.3 in patients who did not use sanitizer with a significant difference between them (p=0.05), as shown in Table I.

All patients were given sucralfate and Nimesulide, 16(24.24%) patients received enoxaparin while 49(74.24%) patients did not receive enoxaparin and found a significant difference between the mean change in oxygen saturation of them (p=0.0001). On the other hand, 47 (71.2%) patients received azithromycin while 19(28.8%) patients did not received azithromycin and found a significant difference between the mean change in oxygen saturation of them (p=0.03). All patients were treated at home except for one patient who required intensive care support and hospitalization. One patient developed left bundle branch block and was referred for cardiac evaluation but managed conservatively. In 34 (51.52%) patients fever settled within 24 hours, in 62 (93.94%) patients, the fever settled within 3 days. The mean spO2 after 5 days was 95.9±3.0, as shown in Table II.

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RESULT

Table I: Demographic Characteristics of the study patients (n=66)

	Groups	Mean±SD Baseline SPO2	p-value
Gender	**Male (n=35)**	92.83±6.41	0.75
	Female (n=31)	93.13±9.39	
Age (years)	**50 years or less (n=31)**	93.94±9.4	0.64
	> 50 years (n=35)	92.11±6.25	
CRP (mg/L)	**5.0 or less (n= 28) normal**	93.4±10.15	0.78
	> 5.0 (n= 30) diseased	92.63±6.0	
D-Dimers (ng/mL)	**250 or less (n=24)**	95.25±3.91	0.025
	More than 250 (n=30)	92.57±5.92	
TLC (WBC/microliter)		7825±3.37	0.248
Use of Mask	**Yes (n=32)**	92.28±9.75	0.44
	No(n=34)	93.62±5.68	
Use of Sanitizer	**Yes(n=36)**	94.72±4.46	0.05
	No (n=30)	90.87±10.34	

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Table II: Mean change in Oxygen Saturation with Nimesulide treatment after five days.

	Status	Mean±SD Change in SPO2	p-value
Oxygen Saturation	**Baseline: 93%±7.9**	3.2 % ±5.9	<0.001*
Diabetes	**Yes (n=22)**	1.55±0.55	0.03*
	No (n=44)	3.68±1.02	
Hypertension	**Yes (n= 28)**	2.29±0.7	0.233
	No (n= 38)	3.47±1.1	
Enoxaparin	**Yes (n=16)**	8.1±9.4	<0.001*
	No (n=49)	1.36±2.46	
Azithromycin	**Yes (n=47)**	3.8±6.57	0.03*
	No (n=19)	0.8±2.19	

(* = Significant p-value)

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DISCUSSION

Nimesulide inhibits Interleukin-6 potently but does not affect Interleukin-8 levels significantly [27]. It inhibits the production of tumor necrosis factor alpha (TNF alpha) and matrix metalloproteinases as well [28]. Nimesulide-treated mice with acute pancreatitis exhibited reduced levels of Interleukin-6 and Interleukin-1B, along with reduced expression of COX2 in pulmonary tissues [29]. Moreover, our study found that Nimesulide significantly decreased lung inflammation in COVID-19 patients, as shown by the improvement in chest radiographs, conceivably by the inhibition of expression of COX2 enzyme in lung tissues.

Researchers in Wuhan evaluated the clinical route of infection as well as risk factors associated with COVID-19 infection. Patients who survived in the study group had a fever that lasted around 12 days, while it lasted for 13 days in those who died [30]. In COVID-19 infection, persistent high-grade fever reflects the severity of the disease [31] and is an indirect indication of inflammation. In contrast to dexamethasone and tocilizumab, Nimesulide reduced the temperature more rapidly, demonstrating superiority since it impeded the inflammatory reaction by limiting the viremic phase or protected the patient from developing super infections or other undesirable side effects[31]. Our study revealed that Nimesulides not only reduced fever within five days, but also improved oxygen saturation.

Enoxaparin and azithromycin were also shown to have antiviral activity against Respiratory Syncytial Virus, Influenza H1N1, Ebola, Zika, Rhinoviruses, and Enteroviruses in a second study [32]. Several cytokines are inhibited by its immunomodulatory properties during COVID-19 infection. It reduces the development of Interleukin-1B, Interleukin-6, Interleukin-8, Interleukin-10, Interleukin-12, and INF-alpha [33]. We also observed that patients treated with Azithromycin and Enoxaparin had a greater improvement in oxygen saturation in our study. The macrolide antibiotic Azithromycin is used to treat bacterial infections of the respiratory tract. Azithromycin, however, decreases the risk of overwhelming bacterial infection in already injured lungs.

Enoxaparin and Heparin were also studied for their role in covid 19 infection. In COVID-related pulmonary vascular disease, enoxaparin may be helpful in reducing thrombosis risk. Furthermore, it reduces the levels of IL-6 and can possess least immunomodulatory effects.

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Additionally, it is believed to limit viral entry into the cells, thus reducing viral load in the blood [34]. Another retrospective analysis compared the clinical outcomes of Enoxaparin with those of other anticoagulants in 1,113 patients. Enoxaparin was significantly associated with a lower mortality rate [35]. We also found that administration of Enoxaparin significantly reduced the mortality rate associated with Covid-19 infection, consistent with the previously reported studies.

According to Ling Lin and Lianfeng Lu et al., the elevated inflammatory factors and D-dimer on days 7–14 of infection might support the use of low molecular weight heparin (LMWH) as remedial options [36]. As a result of the potential for disseminated intravascular coagulation (DIC) resulting from sepsis, the researchers proposed anticoagulation for COVID-19 infected patients with D-Dimer levels more than fourfold the upper limit of normal (ULN), excluding patients with contraindications to anticoagulation. LMWH at 100 IU/kg twice daily subcutaneously for a minimum of 3–5 days was recommended [36]. As a therapeutic strategy to support anticoagulation for COVID-19 patients, we prescribed 60 mg of enoxaparin instead of heparin once daily for those patients with elevated D-dimer.

The European Society of Cardiology has proposed an anticoagulation algorithm [37], which defines the consideration of anticoagulation strategies. Those with dyspnea, respiratory rate greater than 24 breaths per minute, oxygen saturation less than 90%, high CRP, raised D-dimer levels, and higher fibrinogen levels should be prescribed anticoagulants if they have elevated thrombotic risk [37]. In critical care settings, heparin administered parenterally with close supervision and an active prothrombin time target of 60-85 seconds was recommended. Patients with non-critical conditions should receive enoxaparin 1 mg/kg twice daily subcutaneously, or critical patients should receive heparin injections on a similar schedule [37]. According to this study, 30 (45.5%) patients had elevated D dimer, 30 (45.5%) patients had elevated CRP, and more than half of the patients who were diabetic or hypertensive had oxygen saturation of <90%, and needed to be prescribed Azithromycin 250 mg twice daily along with enoxaparin 60 mg subcutaneously once daily for five days.

We were able to sample an extensive range of patients with covid 19 infection by using the mixed approach of our study. Based on the novelty of the disease and concerns of the patients, we were unable to conduct the study on a large sample. Still, this study may be subject to

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selection and observer bias. Better randomized controlled trials are needed to confirm the results in our study.

CONCLUSION

According to this study, Nimesulide treatment led to rapid defervescence, or a temperature drop in 3 days. In addition, oxygen saturation was significantly higher in patients treated with Azithromycin and Enoxaparin. Moreover, our study suggests that patients with elevated D-dimer levels and elevated CRP levels should be given antibacterial macrolides and anticoagulation.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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