Original Research Article

TO ASSESS 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 was intended to assess the anti-inflammatory, analgesic and antipyretic activity of nimesulides 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 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 fivedays. Furthermore, oxygen saturation was also significantly improved in patients treated with nimesulide.

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

INTRODUCTION

Globally, the COVID-19 disease is a mainconcern about public health, still no medication or vaccines for protection and treatment have been accepted until now, excluding remdesivir that has been currentlyapproved for use in the Japan and USA [1]. COVID-19 presents in changeablephases of patient outcomes that ranges from mild, moderate to severe infection [2]. Though, management of mild/asymptomatic patients occur by isolation at home along with self-medication, moderately ill patients need hospitalization whereas severely infected COVID-19 patients remains need hospitalization with intensive care.[3]Due to the variety of comorbidities and complications in the badly affected patients and the devastatingrapidity of the virulent disease, the schedule of medications in COVID-19 critical care is yet to be consistent.[4]

A lot of clinical researches are continuing. Most of theantiviral and antimalarial medicines for instance lopinavir/ritonavir, and chloroquine (CQ) or hydroxychloroquine (HCQ) derivatives that have revealed antiviral function against SARS-CoV-2 in vitro[5]. As SARS coronavirus diseases are recognized to provoke inflammatory processfollowed by damage of lung tissues in moderate-to-severe infections [6], it is predicted that Immunomodulatory drugs mightgiveadvantage in the management of COVID-19 infections.

However, Nimesulide (N-[4-nitro-2-phenoxyphenyl]-methanesulfonamide) is a therapeutically applicable non-steroidal anti-inflammatory drug (NSAID) (7). Clinically, this group of medicines has been generallyapplied as it possess anti-inflammatory, analgesic and antipyretic activities.(8) As far as the side effects are concerned, most commonly observed side effect of NSAIDs are livertoxicity that has been frequentlyrelated to their uncoupling effects on mitochondria (9). Owing to risk of Hepatotoxicity, nimesulide has been unavailable in the marketplace in many nations such as Belgium, Spain, Finland, United States and Ireland.[10]

Alarming issue has been created that NSAIDs could be linkedto raised chances of undesirable effects particularly used in acute viral respiratory infections as well asin COVID-19 disease.[11] Therefore, there is a need to discover drugs with the most significant immunomodulatory functions. Hence, antibacterial macrolide such as azithromycin (AZM) has a unique and remarkable status in this regard for treatment of COVID-19 infections.It has been explored that AZM has considerable antiviral activities. Its antiviral function has been revealed in opposition tohugegroup of viruses' for instance respiratory syncytial virus, Ebola, Zika, infuenzae H1N1 virus, rhinovirus, and enterovirus[12-16]. Its antiviral function in opposition to respiratory syncytial virus has been described in a randomized trial in newborn babies [17]. Azithromycin possessed a synergistic antiviral activity against SARS-CoV-2 as in combination with HCQ both in a clinical site [18] and in vitro [19]. Azithromycin has additionalstriking therapeutic rolealong with pharmacological characteristics in the exploration for COVID-19treatment. It is widelydispersedin lung tissues showing higher average concentrations in both intracellular and extracellular fluids than in plasma [20]

Other complications that are associated with COVID-19 infections are Coagulopathies [21], predominantlyin critical situations of infection [22]. One of the study determined hematological factors in COVID-19 infections [23]. Researches that are comparing anticoagulation treatments are continuing, thoughdue to the extensiveprevalence and severe infection, it is imperative to assess the more observational facts to quicklycreate proof to directthe treatment [24]. A broad variety of anticoagulantslike Enoxaparin, unfractionated Heparin, and Rivaroxaban are being applied in management of COVID-19 patientsaccording to requirement [25].One of the study reported that the standardized-dosage of Enoxaparin enhances survival rate and diminishes hospitalizations in advanced age of > 50 years in symptomatic ambulatory cases [26].

Multiple studies have been conducted internationally to identify the treatment of Covid 19 infection but it is still a matter of debate. Therefore, this study was intended to assess the effects of nimesulide in Covid-19 patients.

METHODOLOGY

This was an uncontrolled longitudinal study conducted at Pakistan Institute of Medical Sciences Islamabad by using consecutive sampling technique. The duration of the study was about six

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months. A total of 66 patients were enrolled for this study after taking the ethical approval by the ethical committee.

The inclusion criteria involved Adults' ≥ 12 years who were not formerly diagnosed or treated for COVID-19 infection were included in the study. Patients who were sensitive to any of the study group, patients who had contraindications to any of the medicines, active bleeding,having past history of myocardial infarction, Peptic ulcer disease, already taking an NSAID or Nimesulide, unable to follow up for the trial period were excluded from the study.

All the patients received Nimesulide 100 mg two timesa day for five days along with10 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 test (over 500) or other comorbiditieswere prescribed enoxaparin in a dose of 60 mg subcutaneously once daily for five days.

All patients were assessed for baseline spO2 and a chest X-ray that was repeated following 5 days. The Primary outcome was estimated in terms of a percent change in oxygen saturation, hospitalization, or death. Secondary outcomes involved symptomatic improvement of fever following initiation of treatment and any reporting of undesirable side effects by the patients.

Data wasentered and analyzed by using SPSS version 22. The continuous variables such as age, TLC, D-dimerand CRP were estimated as means whereas categorical variables like gender, other comorbidities, and radiological findings were presented in percentages and frequencies. Chi-square test and T-test were applied to assess the significance. P value of <0.05 was considered as 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, majority of the patients 57(86.4%) had bilateral consolidations. COVID PCR or COVID Rapid Antigen was positive in 56(84.0%) of the patients. 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). 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), 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 enoxaparinand 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 azithromycinand 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.

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	

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	

DISCUSSION

Nimesulide is a powerfulblocker of Interleukin 6but effects mildly on Interleukin 8 levels.[27] Regardless of other procedures, it limits the development of TNF alpha (Tumor Necrosis Factor Alpha) and limits the formation of matrix metalloproteinases as well.[28]In a mice model of acute pancreatitis, Nimesulidetreated mice inhibited the progression of acute lung injury by restrainingthe activity of Interleukin 6, Interleukin 1B, and TNF alpha along with blockingthe expression of the COX2 enzyme in lung tissues.[29]As far as our study is concerned; the role of nimesulide is significantly associated with the antipyretic activity by inhibiting the expression of COX2 enzyme in lung tissuesof Covid-19 patients thereby decreases the inflammation of lungs. It also improved the oxygen saturation level.

In a retrospective analysis conducted in Wuhan, investigators assessed the clinical routeof infection along with risk factors of COVID-19 infection. The survived patients in the study group had a fever that ended for around 12 days while 13 days in patients who died.[30] Persistent high grade fever in COVID-19 infection reflects the severity of the disease [31] and showed indication of inflammation indirectly. The use of nimesulide reduce the temperature at a considerably faster pace that showed its superiority over dexamethasone or tocilizumab because it impedes the inflammatory reaction by limiting the viremic phase or protecting the patient to develop super infections or other unfavorableside effects associated with the drugs.[31] In our study, nimesulides not only settled the fever within five days by impeding the activity of COX2 enzyme but also improved the oxygen saturation level. Hence, our study proved the superior activity of nimesulides over other NSAIDs.

Similarly, another research revealed that enoxaparin and azithromycin also has a wide range antiviral function against Respiratory syncytial virus, influenza H1N1, Ebola, Zika, rhinovirus, and enterovirus. [32] It has been observed to exhibits immunomodulatorycharacteristics in COVID-19 infection by its impeding action on numerous cytokines. It reduces the development of Interleukin-1B, Interleukin-6, Interleukin-8, Interleukin-10, Interleukin-12, and INF-alpha.[33] It was also observed in our study that patients treated with azithromycin and enoxaparin had a greater improvement in their oxygen saturation. Azithromycin is a macrolide antibiotic and is suggestedfor the treatment of respiratory tract bacterial infections. However,

azithromycin decreases the occurrence of overwhelming bacterial infection in already injured lungs.

One more research studied the role of Enoxaparin and heparin in covid 19 infection. Enoxaparin mightdecrease the probability of thrombosis and could be helpful in the management of COVID-related pulmonary vascular disease. Additionally, it reduces the levels of Il-6 and can possess leastimmunomodulatory property. Moreover, it is believed that limit the viral entrance into the cells resulting a lesseningof viral load in blood.[34] Another retrospective analysis studied 1,113 patients in which clinical outcomes of Enoxaparin were assessed in comparison with other anticoagulants. Therefore, it was proved by the study that Enoxaparin significantly associated with the lower mortality rate.[35] Our study was also consistent with the above reported studies and revealed that administration of Enoxaparin significantly improved the coagulopathies associated with the Covid-19 infection thereby reducing the mortality rate.

Similarly, another researcherLin et al. emphasized that the elevated inflammatory factors and D-dimer on days 7–14 of the infection might support anticoagulation with prescription of low molecular weight heparin (LMWH) as a remedialapproach [36]. Concerns about the raised chances of disseminated intravascular coagulation (DIC) induced by sepsis, the researchers propose anticoagulation for COVID-19 infected patients with D-Dimer levels more than four folds the upper limit of normal (ULN), excluding those with contraindications to anticoagulation. They suggested a dose of 100 IU/kg of LMWH two times a day subcutaneously, for minimum 3–5 days [36]. Our study was inconsistent with the above mentioned study and reported that those patients had elevated D-dimer needed to prescribe subcutaneous dose of 60 mg of enoxaparin instead of heparin once daily as a therapeutic strategy in order to support anticoagulation for COVID-19 patients

Likewise, the European Society of Cardiology currently suggested an anticoagulation algorithm, [37]that defined the consideration of anticoagulation strategies. For elevated thrombotic risk patients elucidated withdyspnea, respiratory rate more than 24, oxygen saturation less than 90%, high CRP, raised D-dimer levels, and higher fibrinogen levels, are the good indicators for prescription of anticoagulants [37]. In the critical care settings, administration of heparin through parenteral route with close observation along with an active prothrombolastin time target of 60–85 s was recommended. For non-critical conditions, they advocate the dose of enoxaparin

1 mg/kg two times daily subcutaneously or suggested to follow the similar heparin injection forcritical patients [37]. As far as our study is concerned, 30(45.45%) patients had elevated D dimer, 30(45.45%) patients had elevated CRP, and more than half patients had oxygen saturation < 90% along with diabetes and hypertension needed to prescribe azithromycin 250 mg twice daily along with enoxaparin in a dose of 60 mg subcutaneously once daily for five days.

The mixed approach of our study has assures that we have samples extensive range of patients with covid 19 infection. However the study might not be immune from observer and selection bias.

CONCLUSION

This study concluded that Nimesulide treatment resulted in a rapid defervescence i.e. temperature fall in three days. Furthermore, oxygen saturation was significantly improved in patients treated with azithromycin and enoxaparin. Moreover, our study suggested the administration of antibacterial macrolide and anticoagulation in COVID-19 patients who had elevated D-dimer levels and raised CRP levels.

Comment [UL2]: Implication for future study, and implication research

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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