Nitazoxanide as an early treatment to reduce the intensity of COVID-19 outbreaks among health personnel

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Abstract. The use of nitazoxanide has previously yielded successful results *in vitro* against the coronavirus. The aim of the present study was to examine the efficacy of the use of nitazoxanide at an early stage among healthcare workers exhibiting symptoms of COVID-19. This was a prospective study carried out in 2020. Healthcare personnel who presented with COVID-19 symptoms, in different 3 hospitals were invited to take Paramix (nitazoxanide), 500 mg orally, every 6 h for 2 days and then 500 mg twice a day for 4 days. To compare the hospitalization percentage, a group of healthcare workers with a respiratory viral infection without COVID-19 criteria were also followed-up. Over a period of 3 months, 150 healthcare workers (111 women and 39 men) presented respiratory symptoms with COVID-19 criteria (mean age, 36±10.6 years; range, 18-68 years). Only one female medical doctor, one nurse and one male from the auxiliary services had to be hospitalized and one death was registered It was thus concluded that nitazoxanide yielded successful results *in vitro* against previous coronavirus and may prove to be useful against SARS-CoV-2 as an early intervention to avoid complications, decreasing the expected number of hospitalizations among infected healthcare workers.

Introduction

The pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2; COVID-19) is the most severe one faced by humans over the past 100 years. The number of confirmed cases worldwide has exceeded 100 million with the total number of related deaths close to two and a half a million (as of February 10, 2021) (1).

In Mexico, since the first cases were reported in Mexico City and Sinaloa on February 28, 2020, and with the antecedent in both areas having traveled to the Lombardy region in Italy prior to the onset of symptoms (2) and to date February 10, 2021, there have been 1,936,013 confirmed cases with 166,731 deaths.

Healthcare personnel have the potential for direct or indirect exposure to patients or infectious materials (3). Unfortunately, these essential workers fighting the coronavirus pandemic are becoming infected and many succumb to the disease; in the case of Mexico, 20% of all infected individuals in the country are professionals in the health sector (4). Exemplifying the critical situation of this group, during the daily national conference of the pandemic evolution on June 23, 2020, it was stated that of the ~200,000 workers in the healthcare system, 39,032 were COVID-19-positive with 584 deaths noted (5). As previously stated, it is necessary to protect healthcare professionals (6), not only with strict infection-control measures (7) and proper equipment (8), but also by offering early treatment options to reduce the length of infectiousness.

It has been well-established that the exposure of professionals to patients diagnosed with COVID-19 can lead to different clinical outcomes (9). In Mexico, the possibility of determining with precision whether the medical doctor, nurse or healthcare worker has contracted COVID-19 in a specific hospital is more difficult, as these workers frequently work in >1 institution (10).

Conversely, amongst the realistic options available for the treatment of COVID-19, nitazoxanide is a low-cost drug and its circulating active metabolite, tizoxanide, inhibits both RNA and DNA viral replication, exhibiting action against influenza A, respiratory syncytial virus, norovirus, dengue, yellow fever,

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Japanese encephalitis virus, rotavirus, hepatitis B and C, human immunodeficiency virus, SARS and Middle East Respiratory Syndrome, the latter two of which are also coronaviruses (11,12).

The aim of the present study was to demonstrate the effectiveness of prescribing nitazoxanide to healthcare workers from the initiation of COVID-19 symptoms in order to reduce the number of hospitalizations, as well as the proportion of COVID-19-associated fatalities.

Patients and methods

Study design. The present study was a prospective study that was conducted between May 1st and July 20th 2020, and included 3 hospitals of the Health Institute of the State of Mexico: 'Mónica Pretelini Sáenz' Maternal-Perinatal Hospital (HMPMPS), located in Toluca, Mexico; Hospital General de Axapusco (Axapusco, State of Mexico); and Hospital General de Cuautitlán 'José Vicente Villada', Cuautitlán, State of Mexico, Mexico.

The present study was approved by the Research Ethics Committee of HMPMPS (approval no. 2020-04-682), and was performed in accordance with the ethical guidelines described in the Helsinki Declaration (Fortaleza, Brazil, 2013).

Patients. The healthcare personnel who presented with COVID-19 symptoms were invited to take Paramix (nitazoxanide) (Laboratorios Liomont, S.A. de C.V.), 500 mg orally every 6 h for 2 days, and then 500 mg twice a day for 4 days. The proposed dose was based on preprint research by Padmanabhan (13,14). In the case of fever, 500 mg paracetamol every 8 h were administered. As regards sample size, the following formula was used for population calculations:

$$n_0 = \frac{Z_\alpha^2 p(1-p)}{d^2} =$$

where Zα = 1.645, p = the percentage of patients with COVID-19 requiring hospitalization (30%), d = allowed error (5%), n_o = number of healthcare workers with COVID-19 that required treatment in the present study to be representative of the community (n=227).

Knowing the limit of the population, healthcare personnel who presented a direct risk to patients with COVID-19, excluding those without contact with patients, those who were sent home for being at risk of contracting COVID (>65 years of age or with comorbidities), those specialists whose attention was cancelled due to the Hospital conversion into an exclusive COVID health center, added to the decision of administrative work by guards and staff who quit their job, n=445, the following formula was used:

$$n = \frac{n_0}{1+\frac{n_0}{N}};$$

and the sample (n) was representative of the healthcare work force at risk, which was 150 healthcare workers.

Procedure. In HMPMPS, once a healthcare personnel presented with COVID-19 symptoms, they were sent to be evaluated by the Epidemiology Service, and if consistent with SARS-CoV-2 infection, the worker was then sent to the Research Unit to receive a medical prescription. The procedure in the other two hospitals was to name a medical doctor to be in charge of the evaluation and prescription of nitazoxanide.

Table I. Semaphore-type scale of COVID-19 symptoms.

Symptoms	Points
Fever, ≥38˚C	5
Dry cough	5
Headache	5
Dyspnea	20
Arthralgias	1
Myalgias	1
Sore throat	1
Nose discharge	1
Conjunctivitis	1
Chest pain	1
Diarrhea	1
Anosmia	1
Ageusia	1

The drugs were distributed using Soluglob Ikon S.A. de C.V., which offers an automated process for individualized doses of every drug. The affected worker had to go to the Soluglob Pharmacy of their hospital to receive the drug dose after completing the informed consent form that included a semaphore-type scale of symptoms (Table I). The personal data collected from each participant included the following: Address, telephone and cell phone number to allow follow-up for pharmacovigilance.

A quantitative PCR test to confirm infection with COVID-19 was performed at the Public Health Laboratory of the State of Mexico. Other studies that were made according to the clinical status of each worker were blood biometry, chest radiography and computed tomography (CT).

The mobile phones of two Internal Medicine physicians were shared with the healthcare workers of the HMPMPS, and the same process was replicated by providing the mobile number of one Internal Medicine physician in the other hospitals (Axapusco and Cuautitlán), to carry out a telephone follow-up and to implement additional/new measures if necessary.

Statistical analysis. Qualitative variables are represented in percentages and the quantitative variables are presented as the means ± standard deviation using Microsoft Excel 2013 (Microsoft Corporation). Differences between females and males in age and severity were analyzed using a Student's t-test, and a χ^2 test was used to compare categorical variables between both groups. All the calculated P-values were two-tailed. A value of $P<0.05$ was considered to indicate a statistically significant difference. Statistical analysis was performed using the Social Science Statistics online program (socscistatistics.com).

Results

Sociodemographic characteristics. Over a period of 3 months, from May to July, 2020, 150 healthcare workers (mean age, 36±10.6 years; age range, 18-68 years), including 111 females and 39 males, presented with respiratory symptoms that met the COVID-19 criteria. Only 1 female medical doctor,

Table II. General characteristics of the healthcare workers with COVID-19.

Variable	Total population (n=150) (%)	Females (n=111) (%)	Males (n=39) (%)	P-value
Age (years)	36±10.6	35.2±10	37.7±12.3	0.2289
Semaphore-type scale (points)	16±9.8	16.5±1	14.6±8.9	0.2927
Fever, ≥38˚C	44.00	41.44	56.41	0.1062
Dry cough	52.67	56.76	48.72	0.3856
Headache	90.00	95.50	87.18	0.0732
Dyspnea	15.33	17.12	10.26	0.3063
Arthralgias	55.33	59.46	51.28	0.3744
Myalgias	59.33	63.96	53.85	0.2643
Sore throat	62.67	66.67	66.67	Not significant
Nose discharge	38.67	44.14	33.33	0.2382
Conjunctivitis	18.00	18.02	17.95	0.9922
Chest pain	38.00	37.84	43.59	0.5270
Diarrhea	36.00	33.33	46.15	0.1529
Anosmia	14.00	12.61	17.95	0.4087
Ageusia	11.33	9.91	15.38	0.3535

Table III. Adverse outcomes observed with the use of nitazoxanide.

	Sex		
Adverse outcome	Females	Males	P-value
Gastrointestinal disorders (nausea, vomiting, diarrhea, and abdominal pain)	43	8	0.0387
Renal and urinary disorders	4	3	0.2977
Nervous system disorders (insomnia)	1	0	0.5520
Cardiac disorders (tachycardia)	0	1	0.0905
Unspecific symptoms	1	0	0.5520

Table IV. Antibiotics prescription according to sex stratification.

	Sex		
Antibiotic	Females	Males	P-value
Levofloxacin	55	25	0.1170
Azithromycin	18	7	0.8027

1 nurse and 1 male worker in the Auxiliary Services had to be hospitalized, and unfortunately the male nurse (aged 35) passed away. He had obesity grade I, according to the classification of the National Institutes of Health (NIH) (15) and his wife and in-laws also became ill; his mother-in-law also passed away. Eventually, qPCR was performed in 115 healthcare workers, confirming the diagnosis of COVID-19; in the remaining 35 patients, the characteristic lung lesions caused by SARS-CoV-2 were determined by a CT scan.

Outcomes. The mean score in the semaphore-type scale just prior to the commencement of the nitazoxanide administration was 16±9.8 points; as a whole, the most common presenting symptoms were headache (90%), sore throat (62.67%) and myalgias (59.33%). Between the sexes, no significant differences were observed in age (t-value, -1.2085; P=0.228984), or in disease severity (t-value, 1.05579; P=0.292786). Based on the results of the χ^2 test, there were no significant differences in the severity of any of the symptoms assessed (Table II).

As regards adverse outcomes, 47 (31.33%) subjects (39 females and 8 males) reported 61 adverse reactions as follows: Gastrointestinal disorders, 51 (34%); renal and urinary disorders, 7 (4.66%); nervous system disorders, 1 (0.66%); cardiac disorders, 1 (0.66%); and one case with unspecific symptoms (anxiety as symptomatology) (Table III).

The most commonly used supplementary medicines were the following: Paracetamol, 150 (100%); levofloxacin, 80 (53.33%); and azithromycin, 25 (16.66%) (Table IV). A CT scan revealed severe lung lesions in 3 cases, and one of these patients required hospitalization. A second case with affected lungs and a persistent fever was treated with meropenem at home with a personal nurse.

Discussion

A previous study demonstrated that the majority of the healthcare workers with confirmed COVID-19 infections were mild cases (16). In another study on healthcare workers, 90% of the affected individuals were not hospitalized; however, they registered 27 deaths, occurring across all age groups; most commonly in those aged ≥65 years (6).

Hospital COVID-19 outbreaks, with several deaths amongst medical doctors, nurses, stretcher handlers, chemists, social workers and administrative staff (17-20), highlight the need for

the management and prevention of further breakouts prior to the acquisition and widespread availability of a vaccine. The study by Wu *et al* (21) suggested that early antiviral treatment significantly attenuated the progression of COVID-19 and improved the prognosis of patients, although some concerns limited the applicability of the results of that study (21).

Other studies have demonstrated significant major outpatient treatment efficacy with the use of hydroxychloroquine alone or of hydroxychloroquine + azithromycin (22). Despite the initial enthusiasm regarding hydroxychloroquine (23), given some major concerns regarding its use and the validity of these early results, there is now strong advice against its use (24,25), increasing the need for studies examining other possible therapeutic options.

Yu *et al* (26) enrolled 129 patients with confirmed COVID-19 (mild to moderate case) who were divided into the early or late antiviral treatment groups. The antiviral drugs, arbidol, interferon, oseltamivir, ribavirin and ganciclovir, were used for the treatment of these patients (26). They concluded that early antiviral treatment could effectively shorten the viral clearance time and prevent the rapid progression of COVID-19. However, a significant difference was observed in the use of glucocorticoids (28.79 vs. 14.29%) between patients with early antiviral treatment and those with late treatment (26).

Specific studies regarding prophylactic measures to manage COVID-19 infections have included Abelson kinase inhibitors (*in vitro*) (27), azithromycin (early use at first signs of infection in adults and children) (28) and cyclosporin A (*in vitro*) (29); however, *in vivo* and among healthcare personnel, hydroxychloroquine has been the most widely evaluated (30). With nitazoxanide, positive results were demonstrated in a phase 2b/3 study for the outpatient management of influenza, in which a 600 mg oral dose b.i.d. of nitazoxanide was associated with a ~1-day improvement in time to resolution of symptoms compared with the placebo group (31).

The approach employed in the present study differs from that of previous studies where they have attempted to treat asymptomatic patients, resulting in controversial results (clinical symptoms vs. viral clearance). Some researchers have supported the notion that antiviral therapy may hasten viral clearance in asymptomatic infections (32).

In the present study, a favorable response to nitazoxanide was observed with regards to fewer hospitalizations, evidencing the benefits of this drug; thus, it was decided to implement this regimen as standard treatment for all workers with COVID-19 symptoms, without waiting for the original date on which the present study was aimed to reach completion (December, 2020), in order to avoid further losses within the healthcare sectors in hospitals.

As regards the prescribed drug, an epidemiological surveillance strategy was deployed, including e-mails, personal supervision at the hospital and telephone follow-up. No suspected cases of glucose-6-phosphate dehydrogenase (G6PD) deficiency were identified amont those taking paracetamol.

Rocco *et al* tested early nitazoxanide therapy against COVID-19, confirming a significant viral load reduction (33). Although in their study, symptom resolution did not differ between the nitazoxanide and placebo groups after 5 days of therapy, the prescribed posology was lower than that proposed to achieve the minimum inhibitory concentration against SARS-CoV-2 (13,14). Novel approaches to regimens with nitazoxanide have included azithromycin mainly (34,35); however, possible synergistic effects with immunomodulants and other types of drugs have also been raised (36,37). In the present study, there were no differences in surveillance adding either azithromycin or levofloxacin. Furthermore, ongoing research has added atazanavir/ritonavir for the treatment of moderate to severe COVID-19 (38) and a number of researchers have indicated that nitazoxanide cannot be ignored as a valid alternative in the current pandemic (39,40,41).

A handicap that the healthcare forces face in Mexico is that the majority of workers do not have social security and work without any types of benefits, and numerous individuals work on temporary contracts. Thus, if healthcare workers are required to isolate, job security should be offered to improve compliance, particularly in cases of severe infections, or in specialized or more renowned hospitals.

This pandemic has revealed several significant inadequacies of healthcare systems worldwide. The impact that this virus has had on the morbidity and mortality of healthcare personnel worldwide is a known and concerning fact. Studies performed in China, Italy, Spain and the United States have demonstrated that between 4-32% of healthcare personnel are infected, with a mortality rate of 3% (42,43,44). Furthermore, meta-analyses have indicated a high prevalence of anxiety (45%), depression (38%), acute stress (31%), burnout (29%) and post-traumatic stress (19%) among healthcare personnel (45,46).

Notably, Mexico is the country with the highest numbers of COVID-19-related deaths amongst healthcare workers. Of the ~7,000 health professionals worldwide who have lost their lives to Covid-19, ≥1,320 were registered in Mexico, according to a report by Amnesty International (47).

Another relevant aspect is the substantial toll this pandemic has had on the global economy, with greater repercussions in countries that traditionally have weaker economies, and the severe and negative impacts it is having on the limited provisions available in these countries.

Finally, conducting a review of the accepted protocols (48,49) for the management of patients infected with COVID-19, several drugs, including antineoplastic, immunomodulatory, antimalarial, non-steroidal anti-inflammatory drugs, antivirals, antimitotics, interferons, vitamins, antibiotics, anticoagulants, antineoplastic agents and steroids, exhibit one common feature, namely that they are generally being used for patients with complications; that is, where the pathogenic process has been given the opportunity to progress to affect multiple systems, which may at least partly explain the discrepancies in the results amongst studies. In addition to the effects of nitazoxanide against viral replication, its administration in experimental animals (12) has been shown to inhibit the cytokine storm caused by the dysregulation of the immune system, which in-turn normally leads to multiple organ dysfunction syndrome and a high mortality rate in critical patients. The advantage of this drug is that it has a good biological profile with minimal side-effects in a low percentage of patients, and it can be administered in individuals as young as 1 years of age, as well as in adults and even pregnant women. Ivermectin, an antiparasitic originally for developed for veterinary use, has recently become a drug of increased interest with regard to COVID-19; however, it cannot be prescribed to children or pregnant women (50), and concentrations required for the inhibition of SARS-CoV-2 are not realistically attainable safely

in humans (51). By contrast, nitazoxanide is safe and effective at a wide range of doses, and is affordable and easily available in several countries and different healthcare institutions.

The present study has some limitations, including the fact that the viral load was not measured, and that this was not a randomized study. However, waiting for a final study that may establish the most efficient early-stage treatment within a certain period of time is not realistic, as this may mean the possible further deaths of hundreds of colleagues, an unaffordable cost.

In conclusion, the results of the present study are promising and demonstrate that nitazoxanide administration may be a useful early intervention against SARS-CoV-2 to avoid complications, reducing the institutional and social viral spread and thus, mortality. It is still undetermined whether a large-scale intervention in families or communities by prescribing nitazoxanide will markedly reduce the spread of SARS-CoV-2. Thus, it is recommended that prescribing nitazoxanide for use against SARS-CoV-2 should be taken into consideration; perhaps, if it is prescribed at a sufficiently early stage, it may convert a potentially fatal infection into an ambulatory and curable disease. Hospitals could track, over a brief time period, the possible effects of nitazoxanide, contrasting the spread and outcomes of healthcare workers treated with this drug against those that did not receive it previously.

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Availability of data and materials

The datasets used during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

HMZ, JMC, JAH and LPC made substantial contributions to the conception and design of the study. JMF, MJVC, HLVA, FMCS, DCH, EMV and ACG were involved in data acquisition. HMZ was involved in data analysis and interpretation. JAH and LPC provided administrative, technical and material support. HLVA, FMCS, DCH, EMV and ACG were responsible for the medical attention of the patients. All authors contributed to the drafting of the manuscript and had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Ethics approval and consent to participate

All patients signed an informed consent form prior to the procedure with current registration with the National Bioethics Commission (CONBIOETICA), as well as by the Research Committee of the same Hospital with current registration in the Federal Commission for Protection against Health Risks (COFEPRIS). The present study was approved by the Research Ethics Committee of HMPMPS (approval no. 2020-04-682), and was performed in accordance with the ethical guidelines described in the Helsinki Declaration (Fortaleza, Brazil, 2013, and according to the level of intervention, it was considered a study of greater than minimal risk. In each case, an informed consent format was applied. ClinicalTrials.gov Identifier: NCT04406246.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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