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Early Treatment Outcomes of SARS-Cov-2 with Ivermectin, Nitazoxanide and Acetylsalicylic Acid in 2 Nursing Homes During The COVID-19 Pandemic in Cali, Colombia

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Abstract

Introduction: The high lethality of COVID-19 among older adults and especially in nursing homes led to the implementation of early treatment for residents in 2 geriatric institutions in Cali, Colombia, where outbreaks of SARS-CoV-2 occurred at different times of the epidemic. Only one of the 475 residents, who was positive for the infection, died of a heart attack.

Objectives: To provide data regarding the early initiation of pharmacological treatment and interdisciplinary monitoring of patients who were RT-PCR-positive or antigen-positive for SARS-CoV-2, as well as to their close contacts. Also, we look for less referrals to hospitals of high-level complexity or to intensive care units, and to contribute to reducing mortality in older adults in nursing homes.

Methods: This is an evaluation of early pharmacological treatment administered to 475 older adults residing in 2 nursing homes, where outbreaks of SARS-CoV-2 were identified by the authorities of each institution. SARS-CoV-2 RT-PCR or antigen tests were performed for all residents. The Rockwood Clinical Frailty Scale (CFS) was taken into account, and the NEWS-2 National Early Warning Score was used to determine which cases should be managed at the institution and which should be referred to a hospital with a higher level of complexity. Interdisciplinary follow-up was carried out by the medical, nursing, psychology and social work staff at the institutions for 30 days. The pharmacological treatment administered to all residents was ivermectin (600 mcg/kg) on days 1 and 7; nitazoxanide (500 mg), BD for 6 days; and acetylsalicylic acid (100 mg) interday, on days 1, 3, 5, and 7.



Results: All 475 residents in 2 nursing homes in Cali, Colombia, were treated when the first positive cases were identified in each institution. Ivermectin, nitazoxanide and acetylsalicylic acid were administered. At the end of the observation period, there were 87 confirmed SARS-CoV-2-positive cases (18.3%); SARS-CoV-2 infection was more common in residents with a frailty scale greater than 5 and with comorbidities such as hypertension, neurocognitive disorder (senile dementia), heart disease and hypothyroidism. Seventy-one residents (15%) remained inside the nursing homes in isolation, and 13 (2.7%) were hospitalized in the respective internal ward. Two patients (0.4%) were referred to institutions with a higher level of complexity of care, and none were referred to the intensive care unit (ICU). The most common side effects of the medications were abdominal pain and diarrhoea. Only one patient who tested positive for SARS-CoV-2 (0.2%) died of a heart attack at 30 days of observation.

Significance: An alternative early therapeutic approach aimed at blocking the replication of the virus in phase 1 of the disease is documented among older adults with comorbidities. Based on the literature, lethality is expected to fluctuate between 24% and 45% in nursing homes. However, herein, the lethality was below 1.1%, indicating a beneficial effect of this approach for this population.

Keywords: SARS-Cov-2; COVID-19; Ivermectin, Nitazoxanide; Acetylsalicylic Acid; Nursing Home; Comorbidities; Frailty Scale

Introduction

Since the beginning of the COVID-19 pandemic caused by the SARS-CoV-2 virus in 2019, international reports showed a high lethality in adults over 60 years of age, being even higher when they reside in nursing homes (NHs). The World Health Organization (WHO) [1], from its European regional office, warned in April 2020 that 95% of deaths occurred in people over 60 years of age and, of these, 50% occurred in people over 80 years of age. Eight of every 10 deaths occurred among people with one or more comorbidities. The Centers for Disease Control of the United States (CDC) [2] estimated that compared to young adults aged 18 to 29 years, older adults between 75 and 84 years of age had an 8 times greater risk of hospitalization and 186 times greater risk of death. Previous studies in NHs in Massachusetts [3,4] showed high mortality among residents with greater frailty. In another study in the United Kingdom in 4 NHs, those infected with SARS-CoV-2 who died were predominantly men with a high prevalence of cardiovascular disease [3-7]. A similar situation occurred in Colombia, with a lethality of 81.8% among those over 60 years of age, whether or not they were institutionalized, a lethality that has remained constant [8].

NHs residents are people with a high degree of vulnerability due to their age, comorbidities and high degree of dependence and frailty, with cognitive and physical impairments with a high risk of acquiring SARS-CoV-2 infection [9,10]. In these NHs, communal areas are shared with little social distancing, an environment conducive to and with a high risk for dissemination, infection and complications [11,12]. COVID-19 cases were present in 2 NHs in Valle del Cauca: San Miguel Geriatric Nursing Home (HGASM, for its initials in Spanish) and the Nursing Home Foundation (FHG, for its initials in Spanish). The risk of infection occurring in these groups was very high, and the probability of referral to the ICU and of death was also high. The absence of a specific treatment to prevent the progression of the disease from phase 1 of viral replication to inflammatory phases 2 and 3 caused an initial feeling of impotence that translated into a challenge to find timely and effective therapies [13,14]. The medical group that led the treatment [16] in these NHs decided to initiate an early treatment to all contacts and caregivers of those patients positive to SARS-CoV-2/COVID-19 with ivermectin,

nitazoxanide and acetylsalicylic acid (ASA). Similar studies [15] with other viruses, such as human immunodeficiency virus (HIV), demonstrated the importance of using multiple drugs at different times of the intracytoplasmic viral replication cycle. Both nitazoxanide and ivermectin are widely used drugs in older adults in NHs, have no significant adverse effects that advise against their widespread use, are very innocuous, and are approved by the US Food and Drug Administration (FDA) as research drugs due to their antiviral effect and viral cytotoxicity against SARS-CoV-1 (demonstrated since 2005) and against SARS-CoV-2/COVID-19 in assays with Vero E6 cells (ATCC-1586 in 2020). Therefore, they have been used in NHs around the world, and clinical studies have been initiated to clarify their efficacy against SARS-CoV-2 [17-19].

Nitazoxanide is an antiparasitic with broad spectrum antiviral activity and with good cardiac, renal and hepatic safety profiles. *In vitro*, a mechanism of action has been identified that tends to improve the immune response to COVID-19 through positive feedback to the production of interferon, blocking viral maturation by compromising the trafficking of the virus in different intracellular vacuoles, such as in phagosomes and the Golgi apparatus and, possibly, in the rough endoplasmic reticulum, in addition to probably compromising the insertion of the viral protein in the extracellular membrane before viral budding [20, 21]. There is no restriction for use in older adults.

The following mechanisms of action account for the antiviral actions of ivermectin *in vitro*:

- Ivermectin blocks the CD147 protein, co-receptor of ACE2, for spicule cleavage and endocytosis of the virus.
- Ivermectin tends to dissociate the preformed nuclear importin heterodimer IMP- α / β 1, which is responsible for the transport of viral inhibitory proteins into the cell nucleus, allowing normal intracellular mechanisms to limit viral growth and secondarily increase the production of interferon.
- Ivermectin decreases the formation of erythrocyte aggregates when interacting with platelets, thus preventing vascular micro thrombosis, a phenomenon observed in pathology studies of deceased patients with COVID-19. It has been administered

worldwide in more than 3,200 million doses in Africa, Latin America and Asia, with very few serious adverse effects [21-23].

- In addition, taking into account the findings of different studies that show the phenomenon of massive thrombosis, both in the microvasculature and in large vessels, the addition of ASA as an antiplatelet agent tends to reduce and prevent this complication. Furthermore, ivermectin intervenes in coagulation factors II and VII, thereby improving the antiplatelet action of ASA, enhancing the prevention of one of the main complications, i.e. massive micro thrombosis, documented for COVID-19 [24-26]. Notably, this drug has been widely used in NHs and in groups of older adults, with known adverse effects.

The medical group that led the intervention considered the following bonding criteria for the implementation process:

- Early initiation of medication in older adults with a positive test for SARS-CoV-2 and their close contacts in the nursing home where they reside, regardless of their SARS-CoV-2 status.
- Guaranteed interdisciplinary monitoring based on a consensual model.
- Reduce referrals to higher complexity of care hospitals and intensive care units.
- Contribute to reducing morbidity and mortality from COVID-19 among household residents.

Biosecurity actions (social distancing, hand washing and use of face masks) delayed the appearance of the outbreak for several months in both institutions. This article documents the number of referrals to the ICU and deaths among individuals with SARS-CoV-2 and their contacts in 2 NHs in Cali, Colombia, during a 30-day period.

Materials and Methods

An observational analysis was performed in 2 NHs in Cali, Colombia, with individuals with SARS-CoV-2 and their contacts for 30 days. Symptomatic residents were identified as having confirmed SARS-CoV-2 cases when RT-PCR or antigen tests were positive. Subsequently, all contacts and caregivers were identified, and diagnostic tests were performed. Taking into account that the opportunity to deliver the test results was on average 8 days, the medical group decided to initiate early therapeutic treatment for all individuals with suspected cases, their contacts and their caregivers. The following ethical and pharmacological criteria were taken into consideration as decisions for the implementation: a) for admission to the institution, the resident or their legal representative signed an authorization form for the medical staff to prescribe the required medication based on the disease status of each person; therefore, informed consent was not required because this study was not a clinical trial but a therapeutic approach; b) the study was conducted in accordance with the Declaration of Helsinki [27], paragraph 37, given the high vulnerability and risk of death of older adults, respecting the right of patients to receive the therapy that, based

on the available scientific literature, would have the best possible efficacy and lowest risk of side effects, and c) ivermectin, nitazoxanide and acetylsalicylic acid are medications that are usually given to NHs residents, all are highly innocuous.

The medical group organized the therapeutic approach, based on the following components:

- Training meetings or interdisciplinary studies on SARS-CoV-2/ COVID-19 for the entire team of caregivers, professionals and assistants of the health team as well as operational and administrative workers at the institutions – With their support, direct communication and review of clinical history records and daily census were maintained.
- Revision of the Rockwood CFS [10,28], with which older adults are administered upon admission, allowing each resident to be assigned, based on the guidelines of each institution, the corresponding ward for their best safety and care - The CFS scale, with a score that ranges from 1 to 9, classifies those from 1 to 4 as with total independence or limitations in their physical mobility, and from 5 to 9 assess the deterioration of mobility begins and progression towards total or almost terminal dependence. Not necessarily every resident progresses through the scale 1 to 9; it depends on each individual and the care offered.
- Early identification of virus infection using RT-PCR or SARS-CoV-2 antigen tests applied to all residents, their contacts and their caregivers – Patients with a positive result underwent strict isolation, attended by trained healthcare professionals, including the application of the National Early Warning Score NEWS-2 [29].
- Early treatment was ordered for residents with a positive laboratory and their close contacts, with the following schedule: a) ivermectin 0.6% oral solution, 600 mcg/kg/dose on days 1 and 7; b) nitazoxanide tablets, 500 mg, once every 12 hours for 6 days; and c) acetylsalicylic acid tablets, 100 mg interday, days 1, 3, 5, and 7. It was guaranteed that the therapies previously prescribed for those who had comorbidities would continue under the supervision of the geriatricians at each institution;
- A first-level hospitalization ward was established for those patients who required additional therapy, oxygen desaturation (dexamethasone, 6 mg; change in acetylsalicylic acid for low-molecular-weight heparin; addition of antimicrobials), and treatment of adverse effects to the medication. Any change in the daily clinical course was reviewed by the institutional interdisciplinary team, with guidance from external specialists; and
- Daily monitoring by institutional operational personnel was continued for 30 days.
- Those with results positive test results were compared with all residents in HGASM and FHG who underwent the diagnostic test. The differences in outcome variables, ICU referral, and death within 30 days of starting treatment were evaluated with the Chi2 test to determine statistical significance.

Outcomes

In the 2 institutions, there were 475 older adult residents: 253 at HGASM and 222 at FHG. Of these, 227 (47.8%) were women, and 248 (52.2%) were men, with an average and median age for

both sexes of 78 years, mode 82 years and range from 45 to 102 years. Among the 475 tests performed, 87 (18.3%) were positive: 60 (69%) to SARS-CoV-2 RT-PCR and 27 (31%) antigens. Of these, 59 (67.8%) occurred at HGASM and 28 (32.2%) at FHG, with equal distribution by sex ($p = 0.4511$) (Table 1).

Table 1: General characteristics of the populations at the nursing homes.

Total population at the nursing homes										
	Total		Female		Male		Age			
							Range	\bar{X}	Me	Mo
Total	475		227	47.8	248	52.2	45-102	78	78	82
HGASM	253	-53.3	125	55.1	128	51.6	55-102	79	79	78
FHG	222	-46.7	102	44.9	120	48.4	45-98	74	77	82
Population at the nursing homes with positive tests										
	Positive laboratory		Female		Male		Age			
							Range	\bar{X}	Me	Me
Total	87		59	67.8	28	32.2	45-100	73	82	82
HGASM	59	67.8	56	94.9	3	10.7	58-100	81	79	78
FHG	28	32.2	3	5.1	25	89.3	45-93	65	75	62

In the 30-day early intervention period, only one resident died, with a diagnosis of acute myocardial infarction at day 21, 14 days after finishing his treatment cycle, within the follow-up time. Therefore, it was accepted that his death was due to COVID-19, without a treatment effect. The identified comorbidities were basically the same as those described in other studies, such as arterial hypertension (46%), chronic kidney disease (18%), hypothyroidism (16%), diabetes mellitus (13%) and others. There were 26 patients with neurocognitive disorder, of whom 23 were at HGASM and 3 were at FHG ($\text{Chi}^2 = 13.7, p = 0.0002$).

Among the 475 residents, there were 124 (26.1%) residents without comorbidities; 115 (24.2%) with 1 comorbidity; 148 (31.2%) with 2; 60 (12.6%) with 3; and 28 (5.9%) with 4 or more. Among those with 1 or more comorbidities, the likelihood of having a positive test was significantly higher than that for those without any comorbidities ($\text{Chi}^2 = 27.21; p = 0.00000$). Of the 87 residents with a positive test for SARS-CoV-2, there was an association with dementia, statistically significant in 21 residents (24.1%; $p = 0.000$), 6 of whom had heart disease (6.9%; $p = 0.0435$) (Table 2).

Table 2: Comorbidities in residents and SARS-CoV-2-positive cases.

	Total residents		SARS-CoV-2 positive		p
	475		87		
	n	%	n	%	
HBP	217	45.7	40	46.0	0.9516
Dementia	26	5.5	21	24.1	0.0000
Hypothyroidism	75	15.8	17	19.5	0.2884
DM	62	13.1	11	12.6	0.9003
COPD	44	9.3	11	12.6	0.2288
Chronic kidney disease	84	17.7	11	12.6	0.1727
Heart disease	16	3.4	6	6.9	0.0435
Obesity	28	5.9	5	5.7	0.9484
Alcoholism	11	2.3	3	3.4	0.4371
Cancer	1	0.2	1	1.1	0.0345
Other	3	0.6	0	0.0	NA

Regarding the CFS, 149 (31.4%) residents had scores between 1 and 4, and 326 (68.6%) had scores between 5 and 9. Among the 87 residents positive for SARS-CoV-2, 27 (31%) had scores less than 4, while 60 (69%) had scores greater than 5. Among those with frailty scores between 5 and 9, the likelihood of having a positive test

at HGASM (Chi2 4.75; p: 0.029) and FHG (Chi2 = 8.54; p = 0.003) was significant. There was a significant association between the sex distribution and CFS scores among those with positive SARS-CoV-2 tests (Chi2 = 17.12; p = 0.0000) (Table 3).

Table 3: Frailty scale in SARS-CoV-2-positive residents.

	1	2	3	4	5	6	7	8	9	Total
F	0	2	4	2	5	10	12	22	2	59
M	4	3	8	4	9	0	0	0	0	28
40-59	0	0	1	1	0	0	1	0	0	3
60-69	2	1	5	1	4	2	2	2	0	19
70-79	1	1	2	2	2	1	4	2	0	15
80-89	0	3	4	2	7	5	3	12	1	37
90-99	1	0	0	0	1	2	1	6	1	12
≥100	0	0	0	0	0	0	1	0	0	1
Total positives	4	5	12	6	14	10	12	22	2	87
	27 (31%)					60 (69%)				

Of the 87 residents positive for SARS-CoV-2, 71 (81.6%) were strictly isolated in the ward assigned to them, and 13 (14.9%) were hospitalized in the NHs ward defined for SARS-CoV-2-positive residents with strict interdisciplinary follow-up; both groups were evaluated as low complexity, without requiring referral to another institution. Two (2.3%) were referred for management in health care institutions (IPSS) with a medium complexity of care, 1 for re-

spiratory symptoms and another for abdominal pain, returning to their NH to continue their management. None were referred to the ICU. During follow-up, only 1 resident died among the 87 residents positive for SARS-CoV-2, for a lethality rate in the 2 NHs of 1.1%. The mortality rate for the 475 residents who received triple therapy was 0.2% (Table 4).

Table 4: Isolation and hospitalization.

		HGASM	FHG
	Isolation	44	27
Level 1	Low complexity IPS hospitalization	13	0
Level 2	Medium complexity IPS hospitalization	2	0
Level 3-4	High complexity IPS/ICU hospitalization	0	0

The most common side effects related to medication were transient diarrhea, abdominal pain, phosphenes and skin rash with improvement in the first 24 hours.

Discussion

This observational study describes the results of early pharmacological treatment with medical follow-up for 30 days in 2 NHs in Cali, Colombia (HASM and FHG). According to the Declaration of Helsinki, paragraph 37 [27], this treatment does not require approval of an Ethics Committee (although it was approved by the IRB of the HGASM) because the drugs used are part of the standard prescription at both NHs, are highly innocuous, and have been effective in other studies. In comparison with the findings of other publications, [4,5,7] among the 475 residents and the 87 residents positive for SARS-CoV-2 tests, the low mortality and the need to re-

fer only 2 residents to medium complexity institutions and none to intensive care units stands out. This finding contrasts with the lethality recorded among adults older than 60 years [8] in the city of Cali (13.8%) and in Colombia (12.9%). Comas et al. [7] reported lethality in NHs in high-income countries between 24% and 45% (average 33.6%), allowing us to assume that among the 87 older adults positive for SARS-CoV-2 in the 2 included HGs, between 21 and 39 residents could have died. Even taking into account the lethality of institutionalized or noninstitutionalized older adults in Cali (13.9%), 12 deaths would be expected. With this intervention, such mortality was avoided, as well as a significant number of referrals to hospitalization and intensive care units [9-11]. The efficacy of the early therapeutic approach was confirmed when the intervention groups, which included individuals of advanced age, were analysed, with increased risk derived from their multiple co-

morbidities, frailty greater than 5, mental disability, confinement and impossibility of maintaining strict social distancing, thus being more exposed and prone to more severe and lethal forms of the disease [4-6,9,10].

This treatment was applied taking into account 4 premises:

- SARS-CoV-2 infection was identified in a timely manner through RT-PCR or antigen testing in high-risk populations to make the decision to start treatment as soon as possible.
- The combined therapies ivermectin [17,18,22-25] and nitazoxanide [19-21] act synergistically in the viral replication cycle. Additionally, acetylsalicylic acid and ivermectin have antithrombotic action. Experience in the management of multiple drugs used in other infectious diseases, especially HIV/AIDS, was taken into account.
- Strict follow-up by multidisciplinary teams guaranteed the continuous evaluation of patients to define the effectiveness of treatment and adverse effects; and
- In a pandemic, therapeutic alternatives should be offered that modify the course of the disease, with drugs tested both in vitro and in vivo.

These drugs, i.e., ivermectin, nitazoxanide and acetylsalicylic acid, are low cost, easy to access and very innocuous. In fact, ivermectin has been widely used in Africa for the control of onchocerciasis, and nitazoxanide has been used for the control of different intracellular parasites, especially in HIV and amoebae in the paediatric population [20,24,30].

Conclusion:

This was an observational study of a treatment applied without a control group and performed under international parameters for this type of intervention. Statistical tests were limited to looking for an association between risk factors and the probability of acquiring SARS-CoV-2 infection in NHs. The greater number of women at HGASM positive for SARS-CoV-2 is explained by the fact that the outbreak began in the women's ward, in women with frailty scores greater than 5 (CFS scale) [28]. A similar situation was observed at FHG, where the men's ward was affected first.

Studies with ivermectin alone or combined with nitazoxanide, azithromycin or chloroquine do not show similar results to those obtained in the 2 NHs studied herein. The possible explanation for this difference is the early initiation of treatment, combined with strict follow-up, because age, comorbidities, and other risk factors were similar to those described in the literature [17,20-22,25]. The results from this study suggest a cause-and-effect relationship between the early pharmacological approach applied to these older adults, low lethality and low referrals for hospitalization and ICU admission. Local, national and international health authorities (including PAHO/WHO), the community and scientific societies are welcome to review this experience, the results of which are encouraging. We are in a position to conduct other complementary randomized controlled trials. Notably, other therapeutic options should be explored, but the result of this intervention lead to the

conclusion that it is possible to treat cases of SARS-CoV-2 early to prevent the progression of infection with various medications, following the recommendations of PAHO/WHO, to investigate therapies via more rigorous methods, such as controlled clinical trials [31].

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Conflict of Interest

No Conflict of Interest.

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