LETTER TO THE EDITOR

Hypertonic saline with xylitol and hyaluronate may shorten the viral shedding duration in asymptomatic COVID-19 positive subjects: a pilot study

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To the Editor,

Coronavirus disease 19 (COVID-19) is a new pandemic that has affected more than 80 million people. COVID-19 is caused by a new coronavirus strain, acute respiratory syndrome coronavirus-2 (SARS-CoV-2). COVID-19 may range from asymptomatic to severe acute respiratory syndrome and coagulative disorder, causing the death of up to 3% of patients (1). However, significant differences exist between countries concerning the incidence, spread, severity, and mortality rates (2).

The World Health Organization defined diagnostic criteria and measures to mitigate and contain the outbreak worldwide. In particular, real-time reverse transcription-polymerase chain reaction (RT-PCR) is the gold standard to confirm COVID-19. Usually, molecular testing requires the collection of a specimen using a nasal swab. Moreover, negative molecular testing also establishes recovery after at least three symptomless days (3). In the general population, screening epidemic outbreaks could reveal asymptomatic COVID-19 carriers in many tested subjects. It is easy to find asymptomatic subjects in the contacts of COVID-19 patients, mainly cohabitants. The health agencies established specific rules to contain the pandemic spread, including isolation for confirmed COVID-19 patients and quarantine for their cohabitants or contacts. Return to the community is possible only after negative RT-PCR testing.

The shedding of viral RNA from respiratory droplets appears to outlast symptoms, and a rapid decline does not always follow seroconversion in viral load. Even asymptomatic COVID-19 may experience a long wait before achieving negative testing. The duration of viral shedding depends on various factors, including the host's ability to clear the virus, viral load, the integrity of the immune system, and therapeutical intervention (4). Moreover, there are discordant outcomes from the relevant studies, i.e., one study reported shedding duration up to 37.8 days after the initial diagnosis (5), and another found immunocompromised patients may prolong viral shedding for two months and more (6).

There is still no specific treatment for COVID-19. The Italian Agency for Drugs (AIFA) released Guide Lines to manage COVID-19 at home (7). This document establishes that symptomless positive subjects do not require any treatment apart from active observation over time. However, as viral

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shedding may persist for a long time, they should observe quarantine also for weeks if not for some months. This fact results in severe social and economic problems.

It has been reported that nasal saline irrigation might be a safe and beneficial remedy in patients with mild COVID-19 (8). Nasal irrigation with hypertonic saline (HS) for the common cold reduced illness duration by 22%, use of symptomatic medications by 36%, and spread into the family by 35%, as well as viral load, as NaCl has an antiviral effect (9). We previously reported that nasal nebulization of a medical device with hypertonic saline (3%) solution, high-molecular-weight sodium hyaluronate 0.2%, and xylitol 5% improved smell dysfunction in COVID-19 patients (10).

As many cohabitants of COVID-19 patients may continue to be positive to RT-PCR testing for an extended period, the current study explored the possibility of shortening the duration of viral shedding in asymptomatic COVID-19 subjects.

MATERIALS AND METHODS

The current study included 172 subjects (80 males and 92 females, aged between 18 and 75 years) with asymptomatic COVID-19 as cohabitants of COVID-19 patients. Inclusion criteria were: adulthood, SARS-CoV-2 infection confirmed by positive molecular testing by nasal swab, the complete absence of symptoms, to be a member of a family with one COVID-19 patient. Exclusion criteria were symptomatic COVID-19, concomitant comorbidity, or current treatment able to interfere with interpretation of the results. The study was performed according to the Helsinki Conference ethical rules, and the internal review board approved the procedure. Each subject signed informed consent.

For nebulization therapy, a medical device was used: a 5 mL solution containing hypertonic saline (3%), high-molecular-weight sodium hyaluronate 0.2%, and xylitol 5% (Aluneb iper, Sakura Italia, Lonato del Garda, Italy). The inhaled therapy was performed using the nasal douche Rinowash (Airliquide Medical System, Italy) that was connected to an aerosol nebulizer with a pneumatic compressor (1.5 bar per 5 L/min) Nebula (Air Liquide Medical Systems, Italy). This nasal device allows the nebulization of particles with a median aerodynamic diameter > 10 microns over a nebulization time of 60-90 seconds for each application. The nebulization therapy was administered twice a day for seven days and started after at least a second positive molecular testing performed one week after the first. Patients were advised to manage the device following hygienic measures to avoid contamination. In addition, the device includes a containment chamber of the liquid returning from the nasal cavities. The nasal swab for molecular testing was repeated after seven days. A group of asymptomatic COVID-19 subjects refused any treatment and served as controls.

RESULTS

The study globally included 172 subjects. Sixteen COVID-19 patients had one cohabitant relative with asymptomatic COVID-19, 24 patients had two positive relatives, and 36 patients had three family members positive for RT-PCR testing. All subjects were positive at the second testing, i.e., on the 14th day. Seventy-two subjects performed therapy from the 7th to the 14th day. All of them were negative at the nasal swab testing performed on the fourteenth day. Sixty-three subjects performed therapy from the 14th to the 21st day. All of them were negative at the nasal swab testing performed on the 21st day. Thirty-seven subjects did not use any medication and were negative on the 28th day. All treated patients completed the therapy. The treatment was safe and well-tolerated in all treated subjects.

DISCUSSION

COVID-19 pandemic affected many people also through healthy carriers. Asymptomatic COVID-19 subjects are contagious as well as symptomatic patients. Moreover, viral shedding can persist for an extended period also in asymptomatic subjects. Nasal irrigation with saline solution is currently the only method that has been recommended in mild COVID-19. At present, only one ongoing study investigated the efficacy and safety of nasal irrigation in outpatients with mild COVID-19 (11). The study compared HS with HS plus 1% surfactant or no intervention. The interim analysis demonstrated that nasal irrigation significantly shortened symptom

duration, mainly concerning nasal congestion and headache. The authors also hypothesized that HS and surfactant could reduce viral shedding.

Subjects positive to the molecular test but without symptoms should be submitted to quarantine and repeat a nasal swab after 14 days. The Italian legislation established only observation for these subjects. The practical problem may occur when a positive test persists for an extended period, causing relevant inconvenience.

The current experience showed that a 7-day course using a medical device containing HS, hyaluronate, and xylitol shortly cleared viral shedding in asymptomatic COVID-19. The intriguing outcome was the rapid viral clearance achieved by the treated participants. Untreated subjects became negative to RT-PCR only after 28 days, whereas treated subjects achieve negativity after one course of topical therapy one or two weeks earlier.

Hypertonic saline solution has many well-known advantages on upper airways, removing secretion and reducing nasal congestion, opening and cleaning the nose, and improving viral clearance, as it has antiviral activity. Hyaluronic acid (HA) has many activities, including activation of innate immunity against viral pathogens, resolution of the inflammatory cascade, moistening respiratory mucosa, and cytoprotection of the epithelial barrier (12). Xylitol exerts an antiviral activity, modulates the immune system, and has decongestant and fluidifying upper airway activity (13). Therefore, these three components provide beneficial effects of this medical device. Moreover, the Rhinowash nasal device contributed to a quick and effective administration of the product. The current outcomes suggest that therapy with a medical device containing HS, HA, and xylitol could shorten viral shedding in asymptomatic COVID-19 subjects.

On the other hand, the current experience has some limitations, including the open study design, the lack of placebo control. This study was preliminary and cannot be considered proof of actual effectiveness in COVID-19 patients. Consequently, further studies should be conducted to answer these unmet needs.

In conclusion, the current experience seemed to suggest that a medical device with HS, HA, and xylitol adequately nebulized into the nose by a specific nasal douche could shorten the time of viral shedding in asymptomatic subjects positive to RT-PCR for RNA of SARS-CoV-2.

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