LETTER TO THE EDITOR

Viral shedding in symptomatic patients with mild COVID-19: an experience with nebulized nasal treatment

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To the Editor,

A new coronavirus strain, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused the most critical pandemic in the last century. Namely, coronavirus disease 19 (COVID-19) has implicated more than 100 million confirmed cases of COVID-19, including almost 3 million deaths, reported to The World Health Organization (WHO). COVID-19 may range from asymptomatic appearance to severe acute respiratory syndrome and coagulative disorder, causing the deaths of up to 3% of patients (1). However, significant differences exist among countries concerning the spread, severity, and mortality rates (2). The WHO defined diagnostic criteria and measures to mitigate and contain the outbreak worldwide. In particular, molecular testing (RT-PCR) by nasal swab is the gold standard to confirm COVID-19.

Negative molecular testing also establishes recovery after at least three symptomless days (3). However, the duration of viral shedding depends on several 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 studies published to date. Agarwal and colleagues retrospectively evaluated 851 COVID-19 patients, reporting a shedding duration up to 37.8 days after the initial diagnosis (5). Positive molecular testing can persist even for a long time; for example, an immunocompromised patient prolonged viral shedding for two months (6).

There is still no specific treatment for symptomatic cases. The Italian Agency for Drugs (AIFA) released Guide Lines for treating COVID-19 at home (7). However, there is no mention of the topical treatment of upper respiratory tract infection. In this regard, nasal saline irrigation might be a safe and beneficial remedy in patients with mild COVID-19 (8). This consideration is derived from a study which demonstrated that nasal irrigation with hypertonic saline (HS) for the common cold reduced illness duration by 22%, use of symptomatic medications by 36%, spread into the family by 35%, and viral load, as NaCl has an antiviral effect (9). Thus, a galenic preparation, containing isotonic thiamphenicol 125 mg diluted in 4 mL in a medical device with saline solution, high-molecular-weight sodium hyaluronate at 0.2%, and xylitol 5%, administered by the nasal douche Rhinowash, reduced symptom perception, spotting, neutrophil, and bacteria count in children with acute rhinopharyngitis (10). More recently, we

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reported that the nebulization of the same medical device restored the olfaction in COVID-19 patients (11). Based on this background, the current study explored the possibility of shortening the duration of viral shedding in patients with mild COVID-19.

MATERIALS AND METHODS

The current study included 76 patients (40 males and 36 females, aged between 31 and 65 years) with mild COVID-19, confirmed by nasal swab positive molecular testing. The inclusion criteria were: adulthood, COVID-19 diagnosis documented by molecular test, and mild symptoms, including fever lower than 37.5°C, dry cough, malaise, and smell and taste impairment, lasting no more than three days. Exclusion criteria were severe COVID-19, requiring hospitalization and pharmacological treatment, concomitant comorbidity, or current treatment which could interfere with the results. The study was carried outaccording to the Declaration of Helsinki, and the internal review board approved the procedure. Each patient signed informed consent for participation.

Nebulization therapy used a galenic preparation, including tobramycin 0.45% and lincomycin 0.75% diluted in 5 mL of a medical device, containing hypertonic saline (3%), high-molecular-weight sodium hyaluronate 0.2%, and xylitol 5% (Aluneb iper, Sakura Italia, Lonato del Garda, Italy), manufactured by Laboratori Farmaceutici Orlandi (Marcianise, Italy). The inhaled therapy was performed using the nasal douche Rinowash (Airliquide Medical System, Italy) 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. The patients were advised to manage the device following hygiene 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 ten days. As each patient had at least one cohabitant positive to the molecular test but symptomless, these subjects were considered controls, as they did not take any medication and repeated, as established by the national rules, the nasal swab after two weeks.

RESULTS

All patients completed the seven-day treatment. At the end of the treatment, all patients were symptomless. The molecular testing, performed on the tenth day, showed that all patients had a negative result. The treatment was safe and well-tolerated in all patients. All cohabitants still had positive molecular testing after 14 days.

DISCUSSION

At present, the Italian Agency for Drugs recommends a “wait and see” strategy for mild COVID-19. However, patients with mild COVID-19 often turn to doctors to have symptomatic treatment to resolve respiratory complaints and become negative to nasal swabs quickly.

The current experience showed that a 7-day course of galenic preparation with two antibiotics (tobramycin and lincomycin) diluted in a medical device containing HS, hyaluronate, and xylitol, shortly cleared viral shedding. On the contrary, all symptomless cohabitants persisted in positive molecular testing at the second nasal swab. At present, only one ongoing study investigated the efficacy and safety of nasal irrigation in outpatients with COVID-19 (12). The study compared HS with HS together with 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.

Topical antibiotic therapy may have advantages as it allows for very low dosage, abating adverse events and resistance, arriving directly at the target organ, and dissolving the biofilm. Even though COVID-19 is a viral disease, topical antibiotics could reduce pathogenic factors promoting viral growth, including post-viral dysbiosis and consequent bacterial super-infection, common during viral infection. 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,

and has additional 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 (13). Xylitol exerts an antiviral activity, modulates the immune system, and has decongestant and fluidifying upper airway activity (14). Therefore, these three components provide added beneficial effects to this medical device. Moreover, the Rhinowash nasal device contributed to a quick and effective administration of the galenic preparation.

The current outcomes could suggest that a galenic preparation with topical vancomycin and lincomycin and a medical device containing HS, HA, and xylitol, nebulized by a nasal douche, could shorten viral shedding in mild COVID-19 patients in comparison with untreated cohabitants who had persistent positive molecular testing.

On the other hand, the current experience has some limitations, including the open study design, the lack of adequate 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 galenic preparation with topical antibiotics, HS, HA, and xylitol adequately nebulized into the nose by a specific nasal device could shorten the time of viral shedding in patients with mild COVID-19.

REFERENCES

1. Johns Hopkins Coronavirus Resource Center. https://coronavirus.jhu.edu/(2020).
2. Kamps BS, Hoffmann C. COVID refernce 2020.5. https://www.CovidReference.com
3. WHO - Country & Technical Guidance - Coronavirus disease (COVID-19) https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance
4. Qu Y-M, Kang E-M, Cong H-Y. Positive result of Sars-Cov-2 in sputum from a cured patient with COVID-19. Travel Med Infect Dis 2020; 34:101619.
5. Agarwal V, Venkatakrishnan AJ, Puranik A, et al. Long-term SARS-CoV-2 RNA shedding and its temporal association to IgG seropositivity. Cell Death Discovery 2020; 6:138.
6. Nakajima Y, Ogai A, Furukawa K, et al. Prolonged viral shedding of SARS-CoV-2 in an immunocompromised patient. J Infect Chemother 2021: 27(2):387-9.
7. AIFA - Farmaci utilizzabili per il trattamento della malattia COVID-19 https://www.aifa.gov.it/aggiornamento-sui-farmaci-utilizzabili-per-il-trattamento-della malattia-covid19
8. Farrell NF, Klatt-Cromwell C, Schneider JS. Benefits and safety of nasal saline irrigations in a pandemic-washing COVID-19 away. JAMA Otolaryngol 2020; 146(9):787-8.
9. Ramalingam S, Graham C, Dove J, et al. A pilot, open-labeled, randomized controlled trial of hypertonic saline nasal irrigation and gargling for the common cold. Sci Rep 2019; 9:1015.
10. Varricchio A, Capasso M, Avvisati F, et al. Inhaled hyaluronic acid as ancillary treatment in children with bacterial acute rhinopharyngitis. J Biol Reg Hom Agents 2014; 28(3):537543.
11. Varricchio A, La Mantia I, Brunese FP, Ciprandi G. Smell recovery in patients with COVID-19: an experience with nebulized nasal treatment. J Biol Reg Hom Agents 2021; 35(2).
12. Kimura KS, Freeman MH, Wessinger BC, et al. Interim analysis of an open-label randomized controlled trial evaluating nasal irrigations in non-hospitalized patients with coronavirus disease 2019. Int Forum Allergy Rhinol 2020; 10(12):1325-8.
13. Jiang D, Liang J, Noble PW. Hyaluronan as an immune regulator in human disease. Physiol Rev 2011; 91(1):221-64.
14. Salli K, Lehtinen MJ, Tiihonen K, et al. Xylitol's health benefits beyond dental health: a comprehensive review. Nutrients 2019; 11(8):1813.