LETTER TO THE EDITOR

Smell recovery in patients with COVID-19: an experience with nebulized nasal treatment

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To the Editor,

Since the initial notification of an unknown pneumonia hotspot in China, more than 80 million confirmed cases of COVID-19, including almost 2 million deaths, have been reported to WHO. COVID-19 is a multifaceted and pleiomorphic disease ranging from asymptomatic cases to severe acute respiratory syndrome, frequently lethal. Olfactory dysfunction is a key symptom in COVID-19 patients and is frequent, as reported by up to 78% of infected subjects (1, 2). Smell impairment may be total, named anosmia, partial, hyposmia, or distorted, cacosmia. Smell defect is very disturbing and could be dangerous. Post-viral smell dysfunction is longer in COVID-19 patients than in patients suffering from the common cold (3). However, anosmia/hyposmia duration is very variable, ranging from a few days to months to persistent.

The recovery of smell depends on different factors, including COVID-19 severity, pre-existing nasal disorders, and host immune response (4). However, a complete recovery of olfaction, such as before the infection, may require a long time. A very recent study reported a persistent loss in 32% of patients, partial recovery in 12%, and total recovery in 39% of patients at a 30-day follow-up (5). Smell impairment is therefore a relevant problem in a great number of COVID-19 patients. Moreover, no specific treatment is currently available. A recent viewpoint recommended nasal saline irrigation as a safe and beneficial remedy in patients with smell impairment dependent on COVID-19 (6). This consideration was derived from a study that demonstrated the ability of nasal irrigation with hypertonic saline (HS) for the common cold (7). HS nasal irrigation reduced illness duration by 22%, using symptomatic medications by 36%, and spreading contagion to the family by 35%. Consequently, the authors suggested that HS use could be a treatment option for COVID-19 (8). The rationale relies on the HS anti-inflammatory and decongestant activity, nasal irrigation removes mucus with entrapped pathogens, restores mucociliary clearance, and NaCl has an antiviral effect. In this regard, a medical device containing saline solution, high-molecular-weight sodium hyaluronate, and xylitol 5%, significantly reduced symptom perception, spotting, neutrophil, and bacteria count in children with acute rhinopharyngitis (9). Based on this background, the current preliminary study explored the possibility of shortening the duration of smell impairment, including anosmia, hyposmia, and cacosmia, in patients with COVID-19.

Key words: anosmia; hyposmia; cacosmia; COVID-19; nebulization; hyaluronic acid; hypertonic saline; xylitol

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MATERIALS AND METHODS

The current study included 42 patients (22 males and 20 females, aged between 22 and 65 years) with COVID-19, confirmed by the nasal swab positive molecular testing. Inclusion criteria were: adulthood, COVID-19 diagnosis, and mild symptoms, including fever lasting no more than three days and lower than 37.5°C, and smell and taste impairment. Exclusion criteria were severe COVID-19, requiring hospitalization and pharmacological treatment, concomitant comorbidity, or current treatment that could interfere with the interpretation of the results. The study was performed according to the Helsinki Conference, and the internal review board approved the procedure. Each patient signed informed consent.

Treatment consisted of nasal nebulization of a solution containing hypertonic (3% NaCl) saline, high-molecular-weight sodium hyaluronate, and xylitol. This solution is available as a medical device (Aluneb® iper, Sakura Italia, Lonato del Garda, Italy). The solution was administered using a medical device (MAD Nasal™, Sakura Italia, Lonato del Garda, Italy). This device is a syringe with a needle able to nebulize particles with an aerodynamic diameter ranging from 30 to 100 mm, ideal for spreading into the upper airways. Namely, the dimensions of particles allows to reach an optimal deposition in the whole nasal cavity up to the nasopharynx.

The patients were evaluated at baseline, that is before initiating the treatment, and at the end of the course. Moreover, patients communicated the end of symptoms on the phone. Olfactory and taste dysfunction were self-reported. Treatment started within seven days after symptom onset. The medication was prescribed twice a day for seven days in patients with hyposmia and ten days in patients with anosmia.

RESULTS

All patients completed the treatment. Globally, 18 patients had hyposmia and hypogeusia, seven of them also had cacosmia; 24 patients had anosmia and ageusia, 10 of them also developed cacosmia during the smell recovery. All patients with hyposmia/hypogeusia improved after treatment and achieved normal sensory function ten days from treatment starting. Cacosmia completely disappeared between 10 and 30 days after the initial administration of Aluneb® iper. All anosmic/ageusic patients recovered normal smell and taste between 10 and 20 days after treatment; cacosmia resolved between 20 and 40 days after treatment onset. The treatment was safe and well-tolerated in all patients. No adverse events were reported during treatment.

DISCUSSION

COVID-19 pandemic is spreading worldwide, affecting many people and claiming many victims. COVID-19 very frequently impairs smell function and is commonly associated with taste impairment. Hyposmia/anosmia and hypogeusia/ageusia are annoying symptoms that severely impact the quality of life. Moreover, sensory alterations tend to persist for a long period. On the other hand, there is no specific treatment for COVID-19 and the cure of olfactory and taste disorders. Nasal irrigation with saline solution is currently the only modality that has been recommended. At present, only one ongoing study investigated the efficacy and safety of nasal irrigation in outpatients with COVID-19 (10). 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 could reduce viral shedding. The present experience showed that a medical device containing HS, hyaluronate, and xylitol, restored sensory function concerning smell and taste. Moreover, this treatment also improved cacosmia, which is usually challenging to be treated.

Hypertonic saline solution has many well-known advantages and can also improve viral clearance. 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 (9). In particular, the virus penetrates the central nervous system across the olfactory mucosa (11). The sustentacular cells play a relevant role in the pathogenic mechanism of smell impairment during viral infection. HA could repair

the viral damage and restore the integrity of the mucosal lining in the olfactory mucosa. Xylitol exerts an antiviral activity, modulates the immune system, and has decongestant and fluidifying upper airway activity (12). Therefore, these three components provide the beneficial effects of the medical device. Moreover, the MAD Nasal™ device used contributed to the effectiveness of successfully nebulizing the solution. In fact, MAD Nasal™ guaranteed an appropriate and effective distribution of the active components across the nasal cavity, allowing to also reach the olfactory mucosa. Moreover, this device was perceived by the patients as comfortable, faster, and easier to use than a traditional aerosol device, as it does not require a pneumatic pump and can be transported very conveniently.

These findings were consistent with three previous studies, investigating the efficacy and safety of hypertonic solution with high-molecular weight HA and xylitol in patients with upper airway disorders (9, 13, 14). Varricchio and colleagues evaluated 51 children with bacterial acute rhinopharyngitis who were randomly assigned to treatment with topical thiamphenicol diluted in isotonic saline alone or isotonic plus sodium hyaluronate with xylitol (9). Both regimens were effective, but the addition of HA and xylitol provided a greater effect on symptom perception, neutrophil count, and bacteria. The study of Cantone and colleagues included 126 children with recurrent respiratory infections (13). The patients were randomly allocated to different treatment groups: isotonic solution plus high-molecular weight HA, isotonic solution with high-molecular weight HA and xylitol, isotonic solution alone, or removing the principal components. The medical device containing HA and xylitol provided the most effective results, considering symptom severity, endoscopic parameters, use of antibiotics and antipyretics. Cioffi and colleagues enrolled 264 children with otitis media with effusion (14). Children were randomly treated with hypertonic solution plus high-molecular weight HA and xylitol or hypertonic solution alone. The medical device, containing the three components provided a significant improvement of the combined clinical score, considering both the intragroup and intergroup comparison.

The current outcomes suggest that nasal nebulization with HS, HA, and xylitol could recover smell and taste impairment in COVID-19 patients. On the other hand, the current experience has some limitations, including the open study design, the lack of a control group, and objective sensory defect measurements. Moreover, the number of cases was limited and severity of smell defects was not considered. Consequently, further studies should be conducted to answer these unmet needs.

In conclusion, the current preliminary experience showed that a medical device with HS, HA, and xylitol nebulized into the nose by a specific device could restore smell and taste in a short time and safely in patients with COVID-19, however, the lack of a control group requires further rigorous studies.

REFERENCES

1. Lechien JR, Chiesa-Estomba CM, De Siati DR, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. Eur Arch Otorhinolaryngol 2020; 277(8): 2251-61.
2. Mullol J, Alobid I, Marino-Sanchez F, et al. The loss of smell and taste in the COVID-19 outbreak: a tale of many countries. Curr Allergy Asthma Rep 2020; 20:61.
3. da Costa KVT, Lins Carnauba AT, Wanderley Rocha, de Andrade KC, Ferreira SMS, Menezes PL. Olfactory and taste disorders in COVID-19: a systematic review. Braz J Otorhinolaryngol 2020; 86(6):781-92.
4. Hoang MP, Kanjanaumporn J, Aeumjaturapat S, et al. Olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. Asian Pac J Allergy Immunol 2020; 38:162-9.
5. Chiesa-Estomba CM, Lechien JR, Radulesco T, et al. Patterns of smell recovery in 751 patients affected by the COVID-19 outbreak. Eur J Neurol 2020; 27(11):2318-21.
6. 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.
7. Ramalingam S, Graham C, Dove J, Morrice L, Sheikh A. A pilot, open-labeled, randomized controlled trial

of hypertonic saline nasal irrigation and gargling for the common cold. Sci Rep 2019; 9:1015.
8. Ramalingam S, Graham C, Dove J, Morrice L, Sheikh A. Hypertonic saline nasal irrigation and gargling should be considered as a treatment option for COVID-19. J Glob Health 2020; 10:010332.
9. Varricchio A, Capasso M, Avvisati F, et al. Inhaled hyaluronic acid as ancillary treatment in children with bacterial acute rhinopharyngitis. J Biol Regul Homeost Agents 2014; 28(3):537-43.
10. 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.
11. Mori I, Nishiyama Y, Yokochi T, et al. Olfactory transmission of neurotropic viruses. J Neurobiol 2005; 11:129-37.
12. Salli K, Lehtinen MJ, Tiihonen K, et al. Xylitol's Health Benefits beyond Dental Health: A Comprehensive Review. Nutrients 2019; 11(8):1813.
13. Cantone E, Cavaliere E, Begvarfaj E, Motta S, Iengo M. New therapeutic strategies for the treatment of recurrent respiratory tract infections in children. J Biol Regul Homeost Agents 2020; 34(3):1185-91.
14. Cioffi L, Gallo P, D'Avino A, et al. Clinical improvement of subacute and chronic otitis media with effusion treated with hyaluronic acid plus hypertonic solution via nasal lavage: a randomized controlled trial. Global Pediatr Health 2017; 4:1-6.