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The Benefits of Oxymetazoline on Sensory Impairment in COVID-19 Patients

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Abstract

The Coronavirus Disease 2019 (COVID-19) outbreak first appeared in Wuhan. Sudden loss of smell and taste sense has become a clinical symptom of COVID-19. One of the evolved and widely used chemosensory examination tools for sensory function is the "Sniffin sticks" test. Potential topical intranasal administration of drugs and agents known to have antiviral properties in SARS-CoV-2. Oxymetazoline is commonly used as a decongestant. Oxymetazoline topical nasal spray showed a viral load-reducing effect on rhinovirus. A randomized pre-post-controlled design consisted of 3 treatment groups. The study was conducted in Makassar in November 2022 until the sample size was met. Statistical analysis used the SPSS 20 program. The results show that there is a significant relationship between CT value and olfactory disorder on the first day using the Mann-Whitney test. On the fifth day, all groups have no significant relationship between CT value and olfactory disorder. In conclusion, comparison of Sniffin stick test scores between treatment groups with Kruskal-Wallis test (0.003) shows that the highest Sniffin stick test score is found of oxymetazoline group (d: 27.83; S: 29.00). The administration of oxymetazoline nasal spray in confirmed COVID-19 patients is more beneficial than the one without oxymetazoline nasal spray (placebo and nasal saline irrigation) in COVID-19 patients with olfactory disorders.

1. Introduction

The Coronavirus Disease 2019 (COVID-19) outbreak started in December 2019 in Wuhan province, China. Structure and Mechanism Coronavirus SARS-CoV-2 is a positive-sense RNA virus with a genome length of approximately 30,000 nucleotides encoding 16 nonstructural proteins and four major structural proteins. The particle is spherical and about 125 nm in size, where the projecting spike glycoproteins form a crown-like appearance responsible for the viral genus. In addition to the spike glycoproteins, the viral corona particle consists of integral membrane proteins E and M, a host-derived lipid envelope, and a helical viral nucleocapsid consisting of N protein and viral genomic RNA. (Higgnis T, Arthur, et all. 2020).

The anatomical parts of the olfactory function involved are the olfactory neuroepithelium, bulbous and olfactory cortex.

The diagnosis of olfactory disorders can be made based on history taking, physical examination, imaging examination, and, in addition, chemosensory examination of the sense of smell.

Many studies suggest that coronavirus infection enters the airway. The virus does not attack neurons but non-neuronal cells that express ACE-2 receptors on airway epithelial cells, microvillar cells, bowman's gland cells, horizontal basal cells and olfactory bulbus. Coronavirus infection spreads from the olfactory epithelium through the cribriform plate, causing cell degeneration and sensory deficits (Cooper W. K. et al. 2020).

The theory is believed to be the transsynaptic transfer of the virus. SARS-CoV-2 can enter the olfactory tract as an early stage of infection. Once SARS-CoV-2 infects the nasal epithelium, it can reach the entire brain and cerebrospinal fluid via the olfactory bulb within seven days and cause inflammatory and demyelinating reactions. This is associated with an olfactory disorders (anosmia) and a gustatory disorders (ageusia) with or without respiratory symptoms. (Zubair AS et all, 2020)

The Sniffin sticks test is a test to assess the chemosensory of the sense of smell with a tool in the form of a pen. This test was pioneered by the olfaction and gustation working group in Germany and was first introduced by Hummel and friends. This test has been used in more than 100 published

Journal of Chemical Health Risks
www.jchr.org
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studies and in many private practice doctors in Europe. (Huriyati E, Nelvia 2014)

The length of the pen is about 14 cm, with a diameter of 1.3 cm, and it contains 4 ml of odorant in the form of a tampon with a solvent of propylene glycol. 7 The examination tool consists of an eye patch, gloves free of odorant, and a pen for the identification test. (Huriyati E, Nelvia 2014)

The total number of pens was 16 triplets (48 pens) for sensory threshold, 16 triplets (48 pens) for sensory discrimination, and 16 pens for sensory identification, making a total of 112 pens (Figure 1) (Huriyati E, Nelvia 2014).

Figure 1. Overall pen for the three types of "Sniffin stick" test

The test was performed by unscrewing the pen cap for 3 seconds and placing the pen 2 cm in front of the nose, depending on whether the left or right nostril was tested. The examination is done by closing the subject's eyes to avoid visual identification of the odorant. From this test, three components can be determined, namely olfactory threshold, olfactory discrimination and olfactory identification. For the olfactory threshold (T), n-butanol was used as an odorant, consisting of 16 serial dilutions at 1:2 in a deionized aqua solvent. This test uses a triple forced choice paradigm, a single-graded method with three answer choices. The test was conducted with n-butanol dilution with the most minor concentration. The score for the sensory threshold is 0 to 16. (Huriyati E, Nelvia T, 2014)

Smelt discrimination (D) is done by randomly using three pens, where two pens contain the same odorant and the third one contains a different odorant. The patient is told to determine which odorant differs from the three pens. The score for sense discrimination is 0 to 16. (Huriyati E, Nelvia T, 2014)

For sense identification (I), the test was performed using 16 different odorants, namely orange, anis (anise), shoe leather, peppermint, banana, lemon, liquorice, cloves, cinnamon, turpentine, garlic, coffee, apple, pineapple, rose and fish. A score of 1 is given for one correct odorant, so the score value for the sense identification test is 0-16. The interval between tests is at least 20 seconds for the desensitization process of the olfactory nerve. (Huriyati E, Nelvia T, 2014)

The TDI score, which results from the three types of "Sniffin sticks" tests, is used to analyze a person's sensory function, scoring 1 to 48. If the score ≤15 is categorized as anosmia, 16-29 is categorized as hyposmia, and ≥30 is categorized as normosmia. This test describes the level of sensory impairment but does not explain the anatomical location of the disorder. (Huriyati E, Nelvia T, 2014)

Oxymetazoline hydrochloride is a sympathomimetic imidazoline amine derivative, commonly used as a topical, also known as an adrenergic drug; it is a class of stimulants that have an agonist effect on the sympathetic nervous system and result in the release and action of nor-epinephrine and epinephrine (adrenaline and noradrenaline). Nasal decongestant drugs such as oxymetazoline can reduce mucosal blood flow and nasal resistance. Under observation for 8 hours, blood flow will drop 30-40% every 6 hours. (Retno SM, zakiah, et all. 2016)

Topical decongestants, include oxymetazoline, can effectively reduce symptoms of obstruction and rhinorrhea in rhinitis; also reported in invitro studies the potential of oxymetazoline to inhibit HRV replication in infected cells, viral eradication effects as well as its ability to protect cells, as well as its effect in suppressing the expression of ICAM-1 (CD54) which is a surface receptor involved in viral invasion and host inflammatory responses. (Retno SM, zakiah, et all. 2016)

Some studies indicate that oxymetazoline may modulate the immediate host response to viral infection. Oxymetazoline has decreased the expression of intracellular adhesion molecule (ICAM) 1 on human umbilical vein endothelial cells after stimulation with apigenin and/or TNF-α. (Winther B, Buchert B, et all. 2010)

Journal of Chemical Health Risks

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Long-term use of oxymetazoline triggers a sensation of nasal congestion due to oedema, hyper-reactivity or a combination of both, which is the mechanism of medical rhinitis. (Retno SM, zakiah, et all 2016)

Based on this background, this article aims to determine the effectiveness of oxymetazoline on nasal disorders in COVID-19 patients in Makassar.

2. RESEARCH METHOD

This research is an experimental clinical trial conducted in humans with a research design in the form of a randomized pre-post-controlled design consisting of 3 treatment groups, in which variables are measured before and after treatment.

2.1 Place and Time of Research

This research was conducted at Hasanddin University Teaching Hospital (RS. UNHAS) and Dr. Wahidin Sudirohusodo Central General Hospital (RSWS). The study will be conducted in November 2022 until the sample size is met.

2.2 Population and Research Sample

The population of this study were anosmia patients who were confirmed positive for COVID-19 by RT-PCR and met the inclusion criteria.

The study sample was anosmia patients who confirmed COVID-19 with RT-PCR who came for treatment at Hasanuddin University Hospital and Dr Wahidin Sudirohusodo Hospital, who met the inclusion criteria and were willing to undergo the Sniffin stick test were included in the study using the consecutive sampling method.

2.3 Sample Size Estimation

The size of each sample was 12 per group to be given a placebo, nasal saline irrigation, and oxymetazoline spray.

2.4 Permission of Research Subjects

In the implementation of this study, each action was carried out with the permission and knowledge of the patient who was made a research participant through an informed consent sheet and declared to meet the ethical requirements to be carried out by the Research Ethics Commission of the Hasanuddin University Teaching Hospital (RS. UNHAS) or Dr Wahidin Sudirohusodo Central General Hospital (RSWS).

2.5 Method of Research

The study was conducted after an explanation was given to the patient, RT-PCR examination of anamnesis, comprehensive ENT examination, sniffing sticks test pre-administration of oxymetazoline therapy, placebo, and nasal saline irrigation and post-administration of therapy, comparing the benefits of administration between treatment groups, statistically analyzing the data obtained.

2.6 Data Analysis

Statistical analysis using the SPSS 20 program. The choice of test depends on the type of variable to be correlated. Numerical data such as age, Sniffin stick test score, and disease duration were tested with paired T test if normally distributed and Mann Whitney U test if abnormally distributed. One-way ANOVA tested nominal data such as gender. Categorical data, such as gender, were tested with the chi-square test.

3. Results and Discussion

Characteristics based on the age of the treatment group in patients with sensory impairment whose average confirmed COVID-19 was given Oxymetazoline was 46, and the nasal saline irrigation group was 46.83, for the placebo group was 48.16. Several studies included in the systematic review by Okosua et al. (2020) reported mean ages ranging from 34.0 to 77.0 years.

Based on gender characteristics, the treatment group in patients with COVID-19 confirmed sensory disorders in the three treatment groups had 25 men (69.5%) and 11 women (30.5%). The majority of the samples in this study were male at 69.5%. A previous study by Rajamani S et al. (2022) in India showed that male participants were more numerous, namely 75% compared to women, in patients infected with COVID-19 and who experienced nasal disorders.

The characteristics of the sample based on the degree of smell impairment based on the Chi-Square test results were significant in the oxymetazoline group at 0.027.

Comparison of Sniffin stick test scores between treatment groups using Oxymetazoline, nasal saline irrigation, and placebo day -1 based on the results of statistical tests with the Kruskal-Wallis test found no significant differences between treatment groups.

Comparison of Sniffin stick test scores between treatment groups using Oxymetazoline, nasal saline irrigation, and placebo day -5 based on the results of statistical tests with

Journal of Chemical Health Risks
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the Kruskal-Wallis test (0.003) found that the Sniffin stick test score was found to be significantly higher in the oxymetazoline group (d: 27.83; S: 29.00). In a randomized clinical trial by Thongngarm et al. (2016), which compared treatments in chronic rhinitis, it was found that patients who received Oxymetazoline had a significant effect on treating anosmia symptoms compared to those who did not receive Oxymetazoline.

A comparison of Sniffin stick test scores dextra and sinistra between the treatment groups using Oxymetazoline, nasal saline irrigation, and placebo day -1, with the Mann-Whitney test, found no significant difference between the treatment groups.

Comparison of Sniffin stick test scores dextra and sinistra between treatment groups using Oxymetazoline, nasal saline irrigation, placebo day -5, the results of statistical tests with the Mann-Whitney test found no significant differences between treatment groups.

Comparison of Sniffin stick test scores dextra and sinistra between treatment groups using Oxymetazoline, nasal saline irrigation, placebo day 1 and 5, statistical tests with Wilcoxon Signed Rank obtained a significant increase in all groups both in the dextra group and the sinistra group.

Comparison of CT value among the three groups using the Kruskal-Wallis test. The statistical test results showed no significant difference in CT value among the three sample groups ($p>0.05$), with the average value of the oxymetazoline treatment group (31.34 ± 7.15), nasal saline irrigation (33.81 ± 4.39), placebo (31.73 ± 4.04).

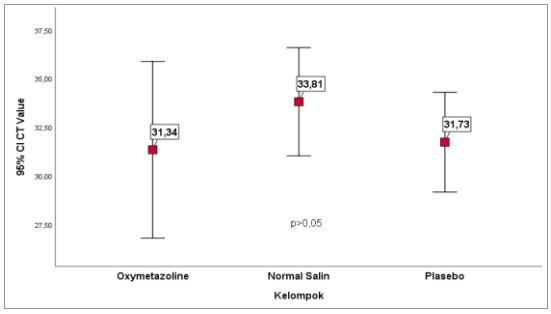

Figure 2. Sample characteristics based on CT value.

There was a significant relationship between CT value and olfactory disorder on day 1 with the Mann-Whiney test, where the mean CT value was higher in Anosmia than in Hyposmia, namely 36.75 compared to 31.71 ($p<0.05$).

The relationship between CT value and olfactory disorder on day five by Mann-Whiney test There was no significant relationship between CT value and olfactory disorder in all groups.

A total of 129 cases were included in the study by Guzainuer A. et al. (2023). Cases without CT value were excluded, and 98 cases were left. CT value was observed daily, analyzed, and compared. The initial CT value from the exposure time to the following days showed that the CT value at the beginning of exposure was more significant, then decreased and reached a minimum value from day 3 to day 10. The CT value gradually increased after day 10. Most had CT values close to 40 after day 20.

4. Conclusion

a. In measuring sensory function using ADI criteria, on the first day of measurement, it was found that all samples experienced sensory disorders, namely Anosmia and Hyposmia.

b. On day five, there was an improvement in the form of normosmia after administering oxymetazoline and nasal saline irrigation.

c. The administration of oxymetazoline nasal spray in confirmed COVID-19 patients is more beneficial than without the administration of oxymetazoline nasal spray (placebo and nasal saline irrigation) in COVID-19 patients with olfactory disorders.

d. There was no significant difference in CT value among the three treatment groups. Both treatments used oxymetazoline, nasal saline irrigation, and placebo.

e. There was no significant relationship between CT value and olfactory disorders.

5. Limitations of the Study

The decline in COVID-19 cases at the time of the study was a limitation of the study's sample.

6. Suggestion

a. Additional variables, such as intranasal corticosteroid administration and olfactory training, are needed.

b. With the development of the COVID-19 virus, it is hoped that there will be further studies based on the symptoms and types of new variants of COVID-19.

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