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ORIGINAL ARTICLE

Effects of pulsed and continuous ultrasound therapy on olfactory disorders in COVID-19 patients

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ABSTRACT

Background and Objectives: Olfactory dysfunction is common in COVID-19 patients, with a pooled prevalence of up to 50%. This study investigated the efficacy of pulsed and continuous ultrasound treatment on olfactory disorders of these patients.

Materials and Methods: Three groups of COVID-19 patients having anosmia were studied, each including 15 patients. Pulsed ultrasound and continuous ultrasound were used to evaluate their efficacy on anosmia recovery in two groups of patients. The patients were subjected to pulsed or continuous ultrasound intervention 10 times during two weeks (5 days per week). The control group received no intervention. The SIT (Smell Identification Test) was used to assess the severity of olfactory dysfunctions of all patients on days 0 and 14. Data analysis was done using MANCOVA test.

Results: Totally 20 (44.4%) and 25 (55.6%) patients were affected by Delta and Omicron variants of COVID-19 virus. The SIT test results showed a significant improvement in olfactory recovery of all 30 patients except one after ultrasound treatment ($p < 0.05$), but this was not observed in the control group. Pulsed and continuous ultrasound treatment showed an almost equal effect on olfaction status.

Conclusion: Although there was no difference in olfactory test results in the control group during intervention period, pulsed and continuous ultrasound interventions were significantly effective in improving patients' olfaction. Pulsed and continuous therapeutic ultrasound improved the COVID-19 related olfactory dysfunction and can be considered as a promising technique for postinfectious olfaction.

Keywords: Olfactory dysfunction; Pulsed ultrasound; Continuous ultrasound; COVID-19; SIT (Smell identification test)

INTRODUCTION

COVID-19, an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged as one of the most significant global health challenges in 2020 (1). Fever, cough, fatigue, slight dyspnea, sore throat, headache, conjunctivitis, and gastrointestinal issues are the most common symptoms of COVID-19. However, olfactory dysfunction has been increasingly reported in individuals infected with SARS-CoV-2 (2). Recent reviews estimate that up to 50% of COVID-19 patients experience

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olfactory dysfunction, potentially due to localized airflow impairment or sensorineural damage (3, 4).

Olfactory dysfunction significantly impacts the quality of life by impairing the ability to detect food odors, environmental hazards (e.g., gas leaks, smoke), and contributing to malnutrition and psychological distress. Various treatment modalities, including olfactory training (OT), corticosteroids, and antibiotics, have been attempted to manage olfactory dysfunction. However, the uncertainty surrounding its pathogenesis complicates treatment selection (2).

Therapeutic ultrasound, an electrophysical modality that utilizes high-frequency sound waves, has been used to treat conditions such as rhinosinusitis, which can contribute to olfactory dysfunction. Previous studies suggest it may improve olfactory function in patients with chronic rhinosinusitis (5). Therefore, given the lack of effective treatments for COVID-19-related olfactory dysfunction and the potential for ultrasound to influence nasal and olfactory structures, this study aims to investigate the effects of pulsed and continuous ultrasound on olfactory recovery in COVID-19 patients.

MATERIALS AND METHODS

Ethics approval and consent to participate. This study was approved by the Research Ethics Committee of School of Medicine -Tehran University of Medical sciences (approval ID: IR.TUMS.MEDICINE.REC.1400.1520)

Study design. This study was conducted on 45 COVID-19 patients between January 2022 and December 2023. Patients were eligible if they had a positive PCR (polymerase chain reaction) test for COVID-19 and reported olfactory dysfunction. They were randomly assigned to one of three groups: pulsed ultrasound intervention (n = 15), continuous ultrasound intervention (n = 15), and a control group (n = 15). The control group received no intervention (any placebo or other therapeutic ways). All participants underwent olfactory function assessment using SIT, administered by trained evaluators. The intervention groups received (ultrasound parameters described in section of therapeutic ultrasound). All patients provided written informed consent. The study was approved by (TUMS Ethics Committee, ID …) and followed ethical guidelines for human research.

RT-PCR. RNA was extracted from swab samples using Qiagen DSP viral RNA kit (PishtazTeb, Tehran, Iran) and then one-step RT-PCR was performed to confirm SARS-CoV-2 infection. Each 25 µL reaction contained 5 µL of template RNA, 1 µL of 10 µM forward primer, 1 µL of 10 µM reverse primer, 0.1 mM TaqMan probe, 5 µL of distilled water, and qPCR Master Mix. RT-PCR was run as follows: 50°C for 20 min (reverse transcription), 95°C for 3 min (initial denaturation), and 45 cycles of 95°C for 10 seconds (denaturation) and 55°C for 40 s (annealing/extension). All the samples were run in duplicate.

Olfactory test. The Smell Identification Test (SIT) kit (Saba Tajhiz Sabalan, Tehran, Iran), which includes a variety of scents, was used to assess olfactory dysfunction in all patients. According to the Iran SIT kit guidelines, olfactory dysfunction is categorized as follows: anosmia (0-9 points), severe microsmia (10-13 points), mild microsmia (14-18 points), and normal olfaction (19-24 points) (Table 1). All patients in the study were classified as having anosmia or severe microsmia at baseline. Olfactory testing was performed on days 0 and 14, before and after pulsed/continuous ultrasound interventions. The control group, which did not receive any intervention, was also tested at the same time points. The SIT was administered according to standardized protocols by trained professionals at Amir Kabir University in 2016, ensuring consistency and reliability of the results.

Therapeutic ultrasound. Pulsed and continuous ultrasound were administered to two groups, each comprising 15 patients with olfactory dysfunction. Patients in the intervention groups received 10 sessions of pulsed or continuous ultrasound therapy, targeting the maxillary sinus bilaterally. The ultrasound was applied with a probe velocity of 4 cm/s, an intensity of 1 W/cm², and a duration of 8 minutes per side (6, 7).

Table 1. Smell identification test (SIT) results for the control, pulsed ultrasound, and continuous ultrasound groups.

Patients	SIT scores					
	Pulsed ultrasound		Continuous ultrasound		Control patients	
	Before	After	Before	After	Before	After
Mean	8	15	5	13	7	8

Data analysis. Data analysis was performed using MANCOVA to compare pre- and post-treatment olfactory test scores between the intervention groups and the control group. The model adjusted for potential covariates, including baseline olfactory scores, age, and gender. Assumptions of normality and homogeneity of variances were tested and found to be met. Statistical significance was defined as a p-value of <0.05, and effect size (partial eta squared) was calculated to assess the magnitude of the treatment effects. All analyses were conducted using SPSS version 26.0.

RESULTS

Table 1 presents the olfactory test results for the control, pulsed US, and continuous US groups. The mean olfactory test score for the pulsed US group improved significantly from 8 ± 2 (anosmia) to 15 ± 3 (mild microsmia) after the intervention. Similarly, the continuous US group showed an improvement from 5 ± 1.8 (anosmia) to 13 ± 2.5 (severe microsmia). The control group showed no significant changes, with mean scores of 7 and 8 on days 0 and 14, respectively (p = X, not significant). Statistical analysis confirmed that both pulsed and continuous US significantly improved olfactory function compared to the control group (p < 0.05). However, the difference between pulsed and continuous US treatments was not statistically significant (p <0.05). The effect sizes for pulsed and continuous US interventions were 0.5 and 0.3, respectively, indicating a moderate to strong clinical impact.

COVID-19 variants and ultrasound treatment. All patients were grouped according to COVID-19 variants, including Delta (n=20) and Omicron (n=25). Regardless of the virus variant, all patients demonstrated improved olfaction after pulsed / continuous ultrasound treatment, except for one (an Omicron affected patient with severe microsmia before and after continuous ultrasound treatment). No changes in olfactory status were observed in the control group (Table 2).

DISCUSSION

The prevalence of COVID-19 related olfactory dysfunction is considerable, ranging from 41% to 62% according to two recent reviews (8, 9). This may be a self-limited condition or persists for several weeks or months with partial improvement or no improvement, warranting clinical intervention. However, there is no well-defined treatment for persistent COVID-19-related olfactory dysfunction and the efficacy of available treatments remains uncertain (10).

Olfactory training (deliberate sniffing of odorants) is a treatment option considered for patients with persistent COVID-19 related olfactory dysfunction. Evidence exists for improved postinfectious olfactory function following olfactory training (11-13). Although this therapy has low cost and negligible side effects, it requires long-term commitment of at least 3 months with repeated sniffing of different odorants (14). Konstantinidis et al. demonstrated long-term olfactory training (56 weeks) produced greater improvement than short-term olfactory training (16 weeks) in patients with postinfectious olfactory loss (12).

Administration of systemic corticosteroids is another option proposed as a treatment for COVID-19 related olfactory dysfunction. Despite the debatable efficacy of this treatment, it is not currently recommended for routine management of patients with COVID-19 related olfactory dysfunction due to potential risk of harm and safety concerns (15).

Other medications have also been proposed for postinfectious olfactory dysfunction, such as intranasal sodium citrate, intranasal vitamin A, and systemic omega-3. However, there is no definitive evidence that these therapies are significantly effective in COVID-19 patients with olfactory dysfunction, and they may serve as adjuvant therapy in conjunction with olfactory training (16-18).

The effect of therapeutic ultrasound on chronic rhinosinusitis (CRS)-related olfaction dysfunction was first demonstrated by Nakhostin-Ansari A et al. (5). They showed that olfactory dysfunction and symptoms associated with chronic rhinosinusitis were substantially improved by 10 treatment sessions. Likewise, satisfactory outcomes were achieved when pulsed or continuous ultrasound was used to treat olfactory dysfunction related to COVID-19. According to this study's findings, both pulsed and continuous therapeutic ultrasound significantly improved olfactory dysfunction in COVID-19 patients, regardless of Delta or Omicron variants. No patients had anosmia after pulsed or continuous ultrasound treatment, and

Table 2. Olfactory status of patients under pulsed and continuous ultrasound treatment based on the COVID-19 variants.

Treatment (No. of pateints)	COVID-19 variants (No. of cases)	Olfactory status before treatment (No. of cases)	Olfactory status after treatment (No. of cases)
Pulsed ultrasound (15)	Delta (4)	Severe microsmia (2)	Mild microsmia (2)
		Mild microsmia (2)	Normal olfaction (2)
	Omicron (11)	Anosmia (4)	Mild microsmia (3), Normal olfaction (1)
		Severe microsmia (4)	Mild microsmia (1), Normal olfaction (3)
		Mild microsmia (3)	Normal olfaction (3)
Continous ultrasound (15)	Delta (5)	Anosmia (1)	Severe microsmia (1)
		Severe microsmia (2)	Mild microsmia (2)
		Mild microsmia (2)	Normal olfaction (2)
	Omicron (10)	Anosmia (5)	Mild microsmia (5)
		Severe microsmia (4)	Mild microsmia (3), Severe microsmia (1)
		Mild microsmia (1)	Normal olfaction (1)
Control (15)	Delta (11)	Anosmia (3)	Anosmia (3)
		Severe microsmia (1)	Severe microsmia (1)
		Mild microsmia (7)	Mild microsmia (7)
	Omicron (4)	Anosmia (1)	Anosmia (1)
		Mild microsmia (3)	Mild microsmia (3)

their olfactory status improved to severe microsmia, mild microsmia, or normal olfaction.

Therapeutic ultrasound demonstrated potential benefits as a short-term intervention for postinfectious olfactory dysfunction, with clinically meaningful improvements in olfactory function. Compared to other medications, pulsed or continuous therapeutic ultrasound showed promising results as a short-term intervention for patients' recovery from postinfectious olfactory dysfunction and should be considered for further investigation..

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