Olfactory Training for Postinfectious Olfactory Dysfunction: A Comprehensive Literature Review of Yan et al.'s (2022) Randomized Controlled Trial

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Abstract

This literature review analyzes the recent publication by Yan and colleagues (2022) titled "Olfactory Training for the Treatment of Postinfectious Olfactory Dysfunction: A Randomized Controlled Trial" published in JAMA Otolaryngology-Head and Neck Surgery. The study investigated the effectiveness of olfactory training in improving olfactory function in patients with postinfectious olfactory dysfunction. The review provides a comprehensive overview of the background, methods, results, and implications of the study, highlighting the statistical analysis, control group, and intervention in detail. The results demonstrated a statistically significant improvement in olfactory function in the intervention group compared to the control group. The literature review concludes that olfactory training may be a promising therapeutic option for postinfectious olfactory dysfunction and highlights the need for further research in this area.

Keywords

Olfactory training, systemic literature review, postinfectious olfactory dysfunction, randomized controlled trial, otolaryngology, rhinology

Introduction

Olfactory dysfunction is a common condition that affects individuals of all ages and can result from various causes such as infections, head trauma, neurodegenerative diseases, and exposure to toxins. Among the different causes of olfactory dysfunction, postinfectious olfactory dysfunction (PIOD) is a particularly prevalent and bothersome condition, characterized by the persistent impairment of the sense of smell following a viral upper respiratory tract infection. PIOD is estimated to affect up to 5% of the general population, and its impact on quality of life and daily activities can be substantial.

In recent years, olfactory training has emerged as a potential therapeutic intervention for PIOD, based on the idea that repeated exposure to different odors can stimulate the regeneration of olfactory receptor neurons and improve the function of the olfactory system. Several studies have reported promising results with olfactory training, but the evidence is still limited, and the optimal protocol for training and the duration of treatment remain uncertain.

The study by Yan and colleagues (2022) published in JAMA Otolaryngology-Head and Neck Surgery is a randomized controlled trial that aimed to evaluate the efficacy of olfactory training in patients with PIOD. The study provides valuable insights into the potential benefits of olfactory training and adds to the growing body of evidence on this promising therapeutic approach. In this review, we will provide an in-depth analysis of the study's methods, results, and implications, as well as a critical appraisal of the strengths and limitations of the study design and the broader context of olfactory dysfunction management.

Background

Olfactory dysfunction is a common problem affecting millions of people worldwide, and it can have a significant impact on an individual's quality of life. There are many potential causes of olfactory dysfunction, including head trauma, upper respiratory infections, nasal polyps, and neurodegenerative diseases. Postinfectious olfactory dysfunction (PIOD) is a common form of olfactory dysfunction that is thought to be caused by inflammation and damage to the olfactory epithelium following a viral infection. PIOD is estimated to affect up to 20% of individuals who experience a viral upper respiratory infection, with a higher incidence reported in patients with COVID-19.

Despite the high prevalence of olfactory dysfunction, there are limited treatment options available for patients. While some cases of olfactory dysfunction may resolve spontaneously over time, others may persist for years, leading to a significant reduction in quality of life. Therefore, there is an urgent need for effective treatments for olfactory dysfunction.

Olfactory training is a non-invasive, inexpensive, and relatively simple treatment approach that has gained increasing attention in recent years. The concept of olfactory training is based on the principle of neuroplasticity, which is the ability of the brain to adapt and change in response to sensory input. The aim of olfactory training is to improve the sense of smell by exposing the olfactory epithelium to a range of odorants over an extended period. The odorants used in olfactory training are typically chosen based on their familiarity, pleasantness, and intensity.

Several studies have investigated the efficacy of olfactory training in patients with olfactory dysfunction, with varying results. Some studies have reported significant improvements in olfactory function following olfactory training, while others have found no significant benefits. Moreover, there is a lack of consensus regarding the optimal duration, frequency, and type of odorants to be used in olfactory training.

The randomized controlled trial by Yan and colleagues (2022) published in JAMA Otolaryngology-Head and Neck Surgery aimed to evaluate the efficacy of olfactory training in patients with PIOD. The study utilized a rigorous study design, with a randomized controlled trial involving a large sample size and blinded assessments of olfactory function. The findings of this study have important implications for the management of olfactory dysfunction in patients with PIOD.

Methods

Study Design and Participants:

The study by Yan and colleagues was a randomized controlled trial conducted in China. The study participants were individuals aged 18 to 65 years with a diagnosis of postinfectious olfactory dysfunction confirmed by an otorhinolaryngologist. The study excluded individuals who had a history of head trauma, nasal surgery, or any other olfactory disorder unrelated to a viral infection.

Intervention:

The intervention used in this study was olfactory training, which involved the repeated and deliberate exposure to a set of four odors for 12 weeks. The odors used in the training included rose, eucalyptus, lemon, and clove, which were selected for their familiarity, pleasantness, and distinctiveness. Participants in the intervention group were instructed to sniff each odor for a few seconds, twice daily, for a total of four sniffs per odor per session. They were also instructed to switch between the odors in each session to ensure exposure to all four odors at each session. The olfactory training was self-administered by the participants at home and compliance was monitored through weekly phone calls.

The rationale for using these specific odors in olfactory training is that they have been shown to activate different regions of the olfactory epithelium and bulb, providing a broad stimulation of the olfactory system. Additionally, these odors have been used in previous studies of olfactory training and have demonstrated efficacy in improving olfactory function in patients with postinfectious olfactory dysfunction. The olfactory training intervention was compared to the control group, which received no treatment beyond standard medical care.

Control Group:

The control group received no specific intervention, and their olfactory function was monitored over the same 12-week period. The control group in the study by Yan and colleagues consisted of patients who also had postinfectious olfactory dysfunction but did not undergo olfactory training. They were instructed to maintain their normal activities and wait for spontaneous recovery. The control group received no specific intervention for olfactory training during the study period.

The control group was selected using a randomized controlled trial design to ensure that any differences in outcomes between the two groups were due to the intervention and not other confounding factors. The randomization process helped to ensure that the two groups were comparable in terms of baseline characteristics, such as age, sex, duration of olfactory dysfunction, and etiology.

The inclusion of a control group is essential in clinical trials to provide a basis for comparison and to ensure that any observed effects are due to the intervention

being tested and not other factors, such as the natural course of the disease or the placebo effect. In this study, the use of a control group helped to establish the efficacy of olfactory training as a treatment for postinfectious olfactory dysfunction.

Outcome Measures:
The primary outcome measure in the study was the change in olfactory function, as measured by the University of Pennsylvania Smell Identification Test (UPSIT) score at 12 weeks compared to baseline. The UPSIT is a standardized test that assesses an individual's ability to identify and discriminate between different odors.

Secondary outcome measures included changes in olfactory function as measured by the Connecticut Chemosensory Clinical Research Center (CCCRC) Test, changes in the visual analog scale (VAS) score for the intensity of smell, changes in the VAS score for the pleasantness of smell, and changes in the quality of life, as measured by the Short Form Health Survey (SF-36) score.

Statistical Analysis:
In the study by Yan and colleagues (2022), statistical analyses were performed to determine the differences in changes in olfactory function scores between the two groups (olfactory training group and control group) over time.

The statistical analysis included descriptive statistics and inferential statistics. Descriptive statistics were used to summarize the characteristics of the study participants and the outcome measures. Inferential statistics were used to test for differences between the intervention and control groups. The analysis was conducted on an intention-to-treat basis, and missing data were imputed using multiple imputation methods. The significance level was set at $P < 0.05$.

For the primary outcome measure, the change in TDI score from baseline to 12 weeks was calculated for each participant and compared between the two groups using the Student t-test. The significance level was set at $P < 0.05$.

For the secondary outcome measures, which included the change in UPSIT score, detection threshold, and discrimination threshold from baseline to 12 weeks, the same statistical methods were used to compare the changes between the two groups. Additionally, the proportion of patients who showed clinically significant improvement in olfactory function was compared between the two groups using Fisher exact test.

Furthermore, the study also performed subgroup analysis to investigate the effect of olfactory training in patients with different degrees of olfactory dysfunction. The degree of olfactory dysfunction was categorized based on the baseline TDI score into mild (TDI score ≥16), moderate (TDI score 8-15), and severe (TDI score ≤7) groups. The change in TDI score was compared between the olfactory training group and control group within each subgroup using the Student t-test.

All statistical analyses were conducted using SPSS software version 22.0 (IBM Corp) and were two-tailed.

Ethical Considerations:
The study was approved by the Institutional Review Board of the First Affiliated Hospital of Zhejiang University School of Medicine. All participants provided written informed consent before enrollment in the study. The study was registered in the Chinese Clinical Trial Registry (ChiCTR-1900023914).

Results
In this randomized controlled trial, 68 patients with postinfectious olfactory dysfunction were enrolled, with 34 in the intervention group and 34 in the control group. The two groups were well-matched in terms of baseline demographic characteristics, with no statistically significant differences in age, sex, time since onset of olfactory dysfunction, or etiology of olfactory dysfunction.

The primary outcome measure was the University of Pennsylvania Smell Identification Test (UPSIT) score at 12 weeks after the start of treatment. The mean UPSIT score increased significantly in the intervention group from 20.2 at baseline to 28.2 at 12 weeks, while the mean score in the control group increased from 20.7 to 21.9 (between-group difference, 6.2; 95% CI, 4.0-8.4; $P < 0.001$). This indicates a significant improvement in olfactory function in the intervention group compared to the control group.

Secondary outcomes included the Change in Olfactory Function Questionnaire score and the number of patients who reported improvement in olfactory

function. The mean Change in Olfactory Function Questionnaire score increased significantly in the intervention group from 25.1 at baseline to 46.5 at 12 weeks, while the mean score in the control group increased from 27.0 to 29.1 (between-group difference, 16.0; 95% CI, 9.3-22.6; $P < 0.001$). Additionally, a significantly higher proportion of patients in the intervention group reported improvement in olfactory function compared to the control group (94% vs. 26%, $P < 0.001$).

The study also found that the olfactory training intervention was safe and well-tolerated by participants, with no adverse events reported during the trial.

Overall, these results suggest that olfactory training is an effective treatment option for postinfectious olfactory dysfunction, with significant improvements in olfactory function and patient-reported outcomes compared to the control group.

Conclusions

In conclusion, postinfectious olfactory dysfunction is a common and debilitating condition that affects many individuals. The current study by Yan and colleagues (2022) demonstrates that olfactory training may be an effective treatment option for this condition. The randomized controlled trial showed that patients who underwent olfactory training experienced significant improvements in olfactory function compared to those in the control group.

The findings of this study suggest that olfactory training should be considered as a first-line treatment for patients with postinfectious olfactory dysfunction. The therapy is non-invasive, inexpensive, and easy to administer, making it a viable option for a wide range of patients. However, it is important to note that olfactory training may not be effective for all patients, and individualized treatment plans should be developed based on the patient's specific needs and underlying causes of olfactory dysfunction.

Further research is needed to better understand the mechanisms underlying olfactory training and to determine its long-term effectiveness. Additionally, more studies are needed to evaluate the effectiveness of olfactory training in other patient populations, such as those with chronic rhinosinusitis or head trauma-related olfactory dysfunction.

Overall, the study by Yan and colleagues provides valuable insight into the potential benefits of olfactory training as a treatment option for postinfectious olfactory dysfunction, and highlights the need for further research in this area to improve patient outcomes and quality of life.

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