International Journal of Otorhinolaryngology and Head and Neck Surgery
Poojary SC et al. Int J Otorhinolaryngol Head Neck Surg. 2026 Aug;12(4):619-624
https://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937
DOI: https://dx.doi.org/10.18203/issn.2454-5929.ijohns20262385

Original Research Article

Comparative efficacy of olfactory training versus combination therapy with oral corticosteroids in COVID-19 associated post-viral olfactory dysfunction

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Received: 05 July 2026
Accepted: 21 July 2026

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ABSTRACT

Background: Post-viral olfactory dysfunction (PVOD) has emerged as a critical public health concern, amplified exponentially by the COVID-19 pandemic. While olfactory training (OT) is the current gold standard for rehabilitation, the additive role of systemic corticosteroids remains controversial, particularly for patients presenting late. This study aimed to compare the efficacy of classical OT alone versus a combination of oral corticosteroids and OT in patients with persistent PVOD.
Methods: A prospective cohort study was conducted at the Department of Otorhinolaryngology in a tertiary care hospital in Mangalore between January 2021 and December 2023. We prospectively enrolled and analyzed 142 patients diagnosed with PVOD lasting >4 weeks. Group A received classical OT alone (n=72), and group B received a 14-day tapering course of oral corticosteroids combined with OT (n=70). Olfactory function was assessed using the "Sniffin' sticks" test (TDI score) at baseline and 12 weeks post-treatment.
Results: Both groups showed significant improvement in TDI scores ($p<0.001$). Group A improved from a mean baseline TDI of 16.4±4.2 to 21.8±5.1. Group B improved from 15.9±3.8 to 24.1±4.9. Inter-group comparison revealed a statistically significant greater improvement in group B (Combination Therapy) compared to group A (OT alone) ($p=0.03$). Clinically significant improvement (increase in TDI ≥5.5) was observed in 34.7% of group A and 48.5% of group B.
Conclusions: While OT remains the cornerstone of therapy, a short course of oral corticosteroids in the persistent phase of PVOD offers significant synergistic benefits. This combination mitigates local neuroinflammation and yields superior olfactory recovery scores, even in sub-acute presentations.

Keywords: Post-viral olfactory dysfunction, Olfactory training, Corticosteroids, Anosmia, COVID-19, Sniffin' sticks

INTRODUCTION

The sense of smell is integral to human quality of life, influencing nutritional intake, safety awareness (e.g., smoke or gas detection), and social interactions.[1] Olfactory dysfunction (OD) affects approximately 5% to 20% of the general population and carries a profound psychosocial burden.[2] Among the various etiologies of OD, PVOD has historically been one of the most common causes, accounting for 18-45% of clinical cases even prior to the COVID-19 pandemic.[3]

The emergence of the SARS-CoV-2 virus, however, exponentially increased the global incidence of PVOD, shifting it from a specialized rhinologic complaint to a widespread public health issue. Sudden onset anosmia was recognized as a cardinal, and sometimes isolated, symptom of the infection.[4-6] In the Indian socio-cultural

context, the loss of smell carries unique dietary and psychological implications; the inability to perceive the complex olfactory profiles of spices and traditional foods leads to a marked decline in appetite and overall well-being. While early clinical efforts during the pandemic focused primarily on managing acute phase of COVID-19 to reduce mortality, long-term complications like chemosensory disorders have now emerged as a significant focus for otolaryngologists. Recent systematic review involving over 4,000 individuals highlighted that remarkable proportion of patients continue to experience persistent dysfunction post-infection for a period ranging from several months to over 2 years.[7]

Pathophysiology of COVID-19-induced PVOD differs slightly from traditional upper respiratory infections. Evidence suggests that SARS-CoV-2 specifically targets sustentacular cells of olfactory epithelium, which heavily express ACE2 and TMPRSS2 receptors, rather than olfactory sensory neurons (OSNs) directly.[8] This targeted attack leads to sudden loss of support for OSNs, initiating a localized cytokine storm, profound neuroinflammation, and subsequent temporary dysfunction. While spontaneous recovery occurs in a majority of patients within 3-4 weeks, an estimated 10-15% suffer from persistent hyposmia or parosmia.[9] This persistence is hypothesized to be driven by chronic, unresolved micro-inflammation or scarring within olfactory cleft, which actively inhibits the regeneration of OSNs.

Current evidence-based management for PVOD is limited. Classical OT, first described by Hummel et al in 2009, involves the deliberate, repeated sniffing of a set of odorants to stimulate neuroplasticity.[10] It is the only intervention with robust level 1A support. However, OT relies purely on endogenous neuro-regeneration, and complete restitution of normosmia is highly variable. Despite European guidelines recommending OT for a minimum of 3 months to maximize the chance of smell improvement, this intervention remains ineffective in 50% to 85% of subjects.[11] Therefore, the search for pharmacological adjuncts has intensified. Consequently, systemic corticosteroids have been theorized to optimize the anatomical microenvironment by reducing mucosal edema and suppressing the localized inflammatory cascade that impedes neuronal repair.[12,13]

The objective of this prospective study was to evaluate and compare the therapeutic efficacy of classical OT alone versus an innovative combination regimen of oral corticosteroids and OT in a cohort of patients with sub-acute, persistent PVOD presenting to a tertiary care center in India.

METHODS

Study design and setting

This prospective cohort study was conducted at the Department of Otorhinolaryngology at a tertiary teaching hospital between January 2021 and December 2023.

Study population

We prospectively enrolled patients presenting to the Rhinology Clinic with a primary complaint of loss of smell (anosmia or hyposmia).

Inclusion criteria

Adult patients (age 18-65 years), clear history of olfactory loss temporally associated with a viral upper respiratory tract infection (URI) or confirmed COVID-19 infection (RT-PCR positive), duration of symptoms persisting for > 4 weeks but < 12 months and agreement to complete baseline and 12-week follow-up olfactory function tests were included in study.

Exclusion criteria

Obstructive nasal pathology (e.g., severe deviated nasal septum, grade III/IV nasal polyposis) confirmed by nasal endoscopy, history of head trauma or neurodegenerative diseases, pre-existing chronic rhinosinusitis (CRS) prior to the viral episode, contraindications to systemic corticosteroids (e.g., uncontrolled diabetes, severe hypertension, glaucoma, active peptic ulcer disease) and inability to complete the 12-week follow-up were excluded from the study.

Intervention groups

Patients were categorized based on their prescribed treatment protocols.

Group A (OT only)

Patients in this arm underwent a structured, classical OT regimen for a duration of 12 weeks. The training utilized four distinct high-concentration essential oils representing the primary odor categories: floral (Rose), resinous (Eucalyptus), fruity (Lemon), and spicy (Clove). Patients were instructed to perform the training twice daily, ideally once in the morning and once in the evening. The prescribed technique involved consciously and deliberately sniffing each odorant for 15 seconds. To prevent olfactory receptor fatigue and habituation, patients were instructed to maintain a strict 15 to 30-second resting interval of normal ambient breathing between each essential oil. Furthermore, patients were counseled to practice 'mindful sniffing'-actively concentrating on the scent, visualizing its source, and recalling past memory associations during the exposure-to maximize top-down cognitive processing and stimulate central neuroplasticity.

Group B (Combination therapy)

Patients who received the same OT protocol plus a short course of oral corticosteroids (Tab. Prednisolone). The starting dose was calculated at 0.5 mg/kg/day and was administered as a single morning dose to mimic the

physiologic cortisol circadian rhythm. The dosage was uniformly tapered over a 14-day period. For a standard 60 kg adult, the step-down regimen was administered as follows: 30 mg/day for days 1 to 4; 20 mg/day for days 5 to 8; 10 mg/day for days 9 to 11; and 5 mg/day for days 12 to 14, followed by complete cessation.

Outcome measures

Primary outcome was change in olfactory function assessed using validated "Sniffin' sticks" test (Burghardt, Wedel, Germany), which evaluates 3 domains.[13-15]

Threshold (T)

The threshold (T) domain was determined using n-butanol staircases.

Discrimination (D)

The discrimination (D) domain measured the individual's ability to distinguish between different smells.

Identification (I)

The identification (I) domain measured the individual's ability to name smells from a forced-choice list.

The sum of these scores yields the TDI score (Range 0-48). A TDI score<16 indicates anosmia, 16-30 indicates hyposmia, and >30 indicates normosmia. A change in TDI score of ≥5.5 points was considered clinically significant.[16]

Statistical analysis

Data were analyzed using SPSS Version 26.0. Continuous variables were expressed as mean±standard deviation (SD). Categorical variables were expressed as frequencies and percentages. Intra-group comparisons were performed using the Paired t-test. Inter-group comparisons were performed using the independent samples t test and Chi-square test. A $p<0.05$ was considered statistically significant (Figure 1).

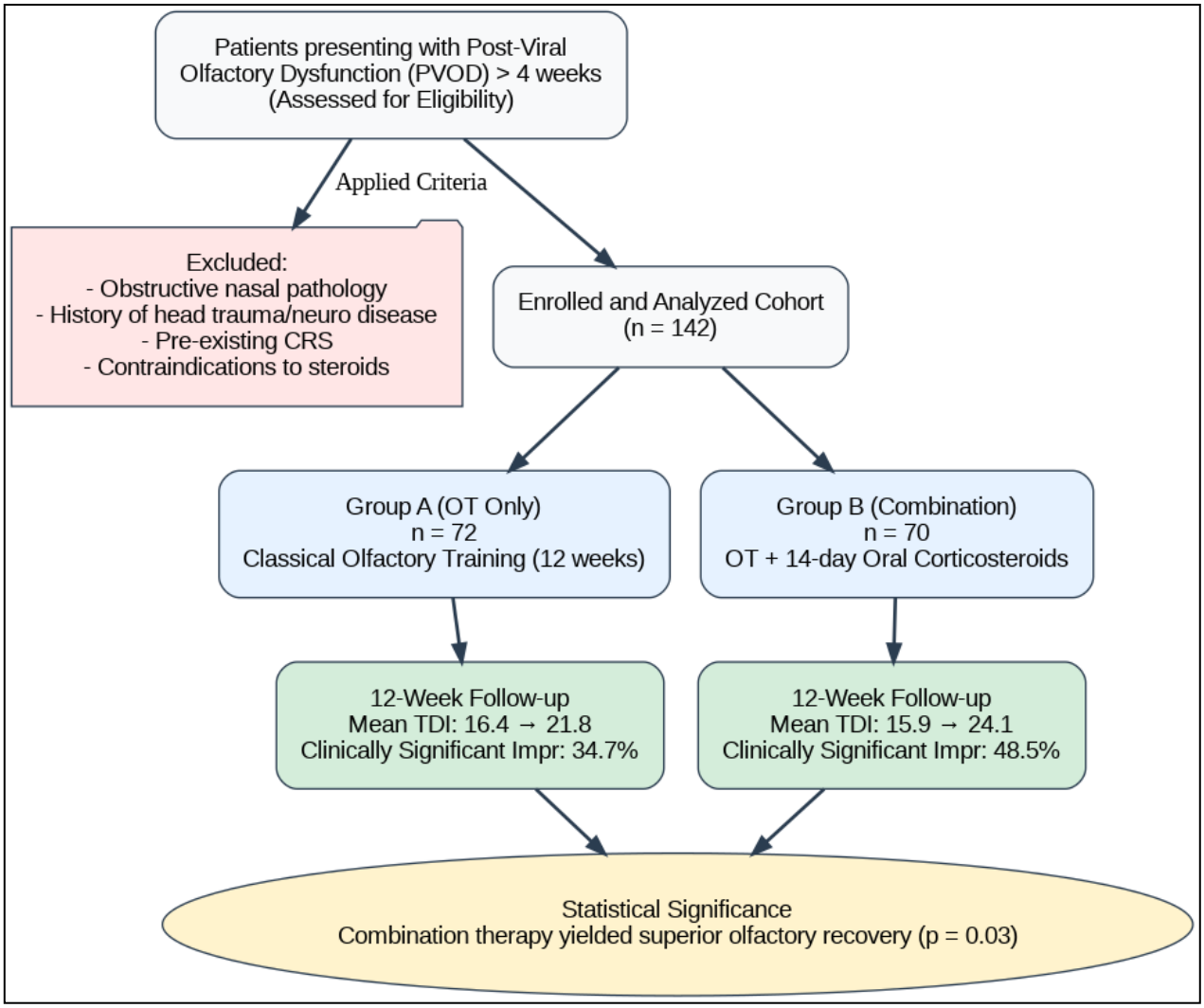

Figure 1: Prospective cohort study illustrating patient enrollment, treatment allocation, and 12 week follow up clinical outcomes.

RESULTS

Demographics

A total of 142 patients met the inclusion criteria and completed the study (Group A: n=72; Group B: n=70). Baseline characteristics are summarized in Table 1. There were no statistically significant differences between the groups regarding age, gender, duration of olfactory loss, or viral etiology (Table 1).

Table 1: Baseline demographic and clinical characteristics.

Characteristics	Group A (OT only), (n=72)	Group B (OT + Steroids), (n=70)	P value
Age (in years)	38.4±10.2	40.1±9.8	0.32
Gender (male/ female)	34/38	31/39	0.78
Duration of OD (Weeks)	9.2±3.1	8.8±3.4	0.46
Etiology: COVID-19	58 (80.5%)	55 (78.5%)	0.77
Baseline TDI score	16.4±4.2	15.9±3.8	0.45
Smoker (yes/no)	8/64	9/61	0.75

Olfactory outcomes

Both groups demonstrated significant improvement in olfactory function after 12 weeks of treatment ($p<0.001$ for both) (Table 2). Group A: Mean TDI increased from 16.4±4.2 to 21.8±5.1. Group B: Mean TDI increased from 15.9±3.8 to 24.1±4.9.

Table 2: Comparison of olfactory outcomes at 12 weeks.

Parameters	Group A (OT Only)	Group B (OT + steroids)	P value (Inter-group)
Baseline TDI	16.4±4.2	15.9±3.8	0.45
12-week TDI	21.8±5.1	24.1±4.9	0.01*
Mean change (Δ TDI)	+5.4	+8.2	0.03*
Clinically significant improvement (Δ TDI≥5.5)	25 (34.7%)	34 (48.5%)	0.04*

*Statistically significant difference ($p<0.05$).

Inter-group comparison

Group B showed a significantly higher mean improvement (Δ TDI: 8.2±3.1) compared to group A (Δ TDI: 5.4±2.8) ($p=0.03$) (Table 2).

Adverse events

In group B, 4 patients (5.7%) reported mild, transient adverse effects (2 gastritis, 1 insomnia, 1 transient hyperglycemia). No adverse events were reported in group A. No patients required discontinuation of therapy.

DISCUSSION

The management of PVOD remains a formidable challenge. Our study aimed to clarify the clinical utility of oral corticosteroids when added to the standard protocol of OT. The results clearly demonstrate that while OT is effective as a standalone therapy, the addition of a short, tapering course of oral corticosteroids significantly enhances both the magnitude and frequency of clinically relevant olfactory recovery in persistent PVOD.

Efficacy and the COVID-19 context

Our findings reinforce the established literature supporting OT, with nearly 35% of group A achieving significant improvement. However, the superior outcomes in group B (48.5% achieving significant improvement) suggest a critical mechanistic synergy. We postulate that this synergy is particularly relevant to COVID-19-induced anosmia. The SARS-CoV-2 virus triggers a highly localized, aggressive inflammatory response in the olfactory cleft upon binding to ACE2 receptors on sustentacular cells. While OT drives neuroplasticity and the regeneration of OSNs from basal cells, the presence of chronic, unresolved micro-inflammation acts as a physical and biochemical barrier.[17] The variable immune response observed in patients might explain why some individuals develop chronic inflammation with immune dysregulation and cell necrosis, thus becoming ideal candidates for targeted systemic steroid therapy. Corticosteroids likely optimize this cellular microenvironment; by mitigating the remnants of the localized cytokine storm, reducing mucosal edema, and clearing inflammatory debris, steroids facilitate the physical access of odorants to the newly regenerating neuroepithelium during training.

Our clinical findings directly align with recent multicenter real-life studies indicating that corticosteroids play a crucial role in the regeneration of the olfactory epithelium when combined with rigorous OT.[18-20] However, it is worth noting that our data contrasts with a few recent systematic reviews that found general corticosteroid use did not show notable efficacy for COVID-19 associated olfactory dysfunction when grouped indiscriminately.[21] This discrepancy highlights the importance of the delivery method; while topical nasal steroids have proven largely ineffective in recent meta-analyses for COVID-19 olfactory dysfunction, oral systemic delivery, as utilized in our protocol, may better penetrate the olfactory cleft to definitively mitigate underlying neuro inflammation.

Challenging the therapeutic window: an innovative perspective

One of the most innovative and clinically vital findings of this study is regarding the timing of intervention. In our cohort, the mean duration of symptoms prior to enrollment was approximately 9 weeks. Traditionally, the "therapeutic window" for systemic steroids in sensorineural losses is considered exceptionally narrow, often restricted to the first 2 to 4 weeks.

However, our prospective data robustly challenges the nihilistic approach often adopted for late-presenting patients. We demonstrated that highly beneficial synergistic effects can still be garnered even after 8 to 12 weeks of symptom persistence. By providing evidence that a sub-acute trial of combination therapy is still highly effective, this study offers a pragmatic, evidence-based protocol for managing the massive backlog of persistent PVOD cases.

The implementation of systemic corticosteroids often raises concerns regarding adverse systemic effects. However, the protocol utilized in this study-a rapid 14-day taper starting at 0.5 mg/kg-yielded a highly favorable safety profile, with only 5.7% of patients reporting mild, transient effects that did not necessitate treatment cessation. This reinforces that when careful patient selection is employed-expressly excluding those with severe comorbidities-the clinical benefits of reversing persistent neuroinflammation heavily outweigh the minimal risks associated with a short-course steroid taper.

While the objective improvement in TDI scores is compelling, the ultimate goal of olfactory rehabilitation is the restoration of patient quality of life. The sudden loss of olfaction profoundly impacts nutritional behavior, personal hygiene, and social engagement, often precipitating depressive symptoms. By accelerating olfactory recovery through the addition of oral corticosteroids, this combination therapy likely plays a pivotal role in mitigating these secondary psychosocial burdens. Future studies must incorporate validated patient-reported outcome measures (PROMs), such as the questionnaire of olfactory disorders (QOD), to rigorously quantify this subjective benefit and bridge the gap between diagnostic precision and holistic patient well-being.

From a global health perspective, the accessibility of a treatment protocol is as critical as its efficacy. Unlike emerging biologic therapies or complex surgical interventions, the combination of classical essential oils and a short, generic course of oral prednisolone is highly cost-effective and readily available. This makes the proposed regimen exceptionally practical for implementation in resource-limited settings. By demonstrating substantial clinical benefit using affordable modalities, this protocol offers a democratized approach to managing the massive global backlog of persistent PVOD cases.

Future directions

The promising synergistic effects observed in our study pave the way for more rigorous clinical investigations. Future research should prioritize multicenter randomized controlled trials (RCTs) with extended follow-up periods to confirm the long-term durability of these olfactory improvements. Additionally, investigating the correlation between objective olfactory scores and targeted biomarkers of neuroinflammation in the nasal mucus could provide deeper insights into the exact mechanisms of corticosteroid efficacy. There is also a need to explore whether different COVID-19 variants respond differently to this combination therapy, given their potentially varying affinities for the olfactory epithelium.

CONCLUSION

PVOD, exacerbated by the COVID-19 pandemic, represents a significant global disease burden. While classical OT remains the foundational treatment, this study provides compelling evidence that a short, tapering course of oral corticosteroids combined with OT delivers superior functional outcomes compared to training alone. We strongly recommend that otorhinolaryngologists incorporate this synergistic regimen for persistent PVOD patients lacking contraindications, moving away from purely expectant management to actively addressing localized neuro inflammation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Poojary SC, Nayak P. Comparative efficacy of olfactory training versus combination therapy with oral corticosteroids in COVID-19 associated post-viral olfactory dysfunction. Int J Otorhinolaryngol Head Neck Surg 2026;12:619-24.