Olfactory Training and Oral CorticosteroidTherapy for Persistent Postinfectious Hyposmia

Gabriel de Souza Mares, Maria Victoria Bastos Tavares, Maria Fernanda Danieluk, Maria Dantas Costa Lima Godoy, Renata Chade Aidar Balasso, Davi Ferreira Soares, Fábio Akira Suzuki

https://doi.org/10.1590/SciELOPreprints.13398

Submitted on: 2025-09-16
Posted on: 2025-09-17 (version 1)
(YYYY-MM-DD)

Olfactory Training and Oral Corticosteroid Therapy for Persistent Postinfectious Hyposmia*

Maria Victoria Bastos Tavares[1] Gabriel de Souza Mares[1] Maria Fernanda Danieluk[1] Maria Dantas Costa Lima Godoy[1] Renata Chade Aidar Balasso[1] Davi Ferreira Soares[2] Fábio Akira Suzuki[1]

[1] Otorhinolaryngology and Cervico-Facial Surgery Service, Instituto de Assistência Médica ao Servidor Público Estadual de São Paulo (IAMSPE), São Paulo, SP, Brazil
[2] Department of Computer Science, CEDS, Instituto Tecnológico de Aeronáutica (ITA), São José dos Campos, SP, Brazil

Address for correspondence Maria Victoria Bastos Tavares, MD, Specialist in Otorhinolaryngology, Otorhinolaryngology and Cervico-Facial Surgery Service, Instituto de Assistência Médica ao Servidor Público Estadual de São Paulo (IAMSPE), São Paulo, SP, Brazil (e-mail: dramariavictoriatavares@gmail.com).

Int Arch Otorhinolaryngol 2025;29(3):s00451802575.

Abstract

Introduction Postinfectious hyposmia gained special attention in the postpandemic era, and persistent cases are particularly difficult to treat. Many unproven therapies are used in clinical practice, including corticosteroids, with insufficient evidence.

Objective To establish the effectiveness of systemic corticosteroid therapy, associated with olfactory training, for persistent postinfectious hyposmia.

Methods Patients with persistent postinfectious hyposmia were divided, based on comorbidities, into control group (submitted to olfactory training alone) and test group (associated 7-day course of prednisone 40 mg). Olfactory evaluations were performed (visual analogue scale, Alcohol Sniff Test, and Connecticut Olfactory Test), at baseline, and at the 3- and 6-month follow-ups.

Results There was no statistically significant difference between the test (n = 10) and control (n = 7) groups ($p > 0.05$) for primary outcomes (visual analogue scale, Alcohol Sniff Test, and Connecticut Olfactory Test), although there was statistically significant improvement of Alcohol Sniff Test scores in both groups at 6 months ($p > 0.05$). The study's statistical power was reduced due to the small sample size. Even without randomization, the groups were not comparable only in terms of age ($p > 0.05$). Although no statistically significant association was found, there was a clear tendency for improvement in the overall olfactory function, which may be spontaneous or due to olfactory training. No side effects were reported.

Conclusion There was no statistically significant benefit of systemic corticosteroid therapy for patients with persistent postinfectious hyposmia ($p > 0.05$). Treatment with systemic corticosteroids should be individualized, and there is no consensus in the literature.

Keywords
- olfaction disorders
- olfactory training
- glucocorticoids

* *Study presented at the 53rd Brazilian National Congress of Otorhinolaryngology, December 1st, 2023.*

received
June 12, 2024
accepted
November 17, 2024

DOI https://doi.org/10.1055/s-0045-1802575.
ISSN 1809-9777.

Thieme Revinter Publicações Ltda., Rua Rego Freitas, 175, loja 1, República, São Paulo, SP, CEP 01220-010, Brazil

Introduction

Olfaction is an important and often undervalued sensory system, contributing to identifying danger, increasing appetite, and influencing human emotion.[1] Its dysfunction is associated with increased risk of food poisoning, smoke inhalation, weight loss, anxiety, and depression.[1] Altered sense of smell is a common symptom in viral respiratory infections. In the post pandemic era, olfactory dysfunctions caught the attention of the scientific community, not only because of their especially high prevalence, but also because of its difficulty to treat.[2,3]

In most cases of postinfectious smell dysfunction, recovery occurs in 2 to 3 weeks, in accordance with the regeneration time of the olfactory epithelium.[2] The mechanisms responsible for postinfectious hyposmia/anosmia include nasal obstruction and alteration of ciliary architecture, preventing the detection of odorants (localized conductive loss); injury to supporting cells or directly to olfactory neurons (sensory dysfunction), that can be caused by viral cytotoxic effect or by secondary immune injury; and injury to the olfactory bulb (central dysfunction).[4] Persistent postinfectious smell alteration may stem from: basal cell damage; viral persistence; or chronic inflammation with immune dysregulation and cell necrosis.[2] A variable immune response would explain why some patients have mild or no smell dysfunction and why others present persistent symptoms.[4] That is also the rationale behind corticosteroid use for treating postinfectious hyposmia.[5] However, there are no studies to date with proven benefit to recommend corticosteroid therapy[6] for postinfectious hyposmia.

The present study aims to establish the effectiveness of systemic corticosteroid therapy, associated with olfactory training, as a treatment for persistent postinfectious hyposmia, both of which are already widely used in otorhinolaryngological practice for the treatment of olfactory losses of various causes.[7–9]

Methods

A monocentric, controlled, non-randomized clinical trial was conducted, without blinding of researchers or patients. It was approved by the institutional Ethics in Research Committee (protocol number 50073721.7.0000.5463), and informed consent forms were signed by all participants.

Adult patients complaining of persistent olfactory alteration for at least 3 months after an upper respiratory infection, followed up at the *Hospital do Servidor Público Estadual*, from July 2021 to January 2023, were included. To this end, an active search was carried out for patients treated for upper respiratory infection with smell complaints, and 1,382 patients were then contacted regarding the persistence of hyposmia.

The exclusion criteria were patients with smell alterations prior to the infection; patients with nasofibrolaryngoscopy abnormalities that may justify olfactory loss from other causes, such as rhinitis; patients without hyposmia or anosmia in the diagnostic olfactory tests; patients without a confirmed upper respiratory infection; patients under 18 and over 70 years of age, who may present age-related smell alterations; and patients who refused to sign the informed consent form.

In the first evaluation, after clinical history and otorhinolaryngological physical examination, patients were submitted to: the Questionnaire of Olfactory Disorders-Negative Statements (QOD-NS) (►**Figure 1**, ►**Appendix 1**), already well established in the literature;10 the visual analogue scale (►**Figure 2**, ►**Appendix 2**); flexible nasofibrolaryngoscopy; the Alcohol Sniff Test (►**Appendix 3**) and the Connecticut Olfactory Test (►**Figure 3**, ►**Appendix 4**), both of which are also well established in the literature.[11,12]

Patients were divided into two groups based on comorbidities and/or contraindications to the use of systemic corticosteroids, such as diabetes and systemic arterial hypertension. The test group, composed of patients without comorbidities, was treated with prednisone 40 mg/day, orally, for 7 days, as established in previous studies,[13] in addition to classic olfactory training,[14] which consists of nasal instillation of 4 fragrances (lavender, eucalyptol/eucalyptus, citronellol/lemon, and eugenol/cloves) for 10 seconds each, 2 times a day, for 6 months. The control group, with patients with contraindications to corticosteroid therapy, underwent classical olfactory training alone.

O Questionário de Proposições Negativas sobre Disfunções do Olfato

Proposições	Pontuação (0 a 3)
Mudanças na minha percepção do cheiro me levam a isolar-me socialmente	
Problemas na minha percepção do cheiro tem um impacto negativo nas minhas atividades sociais	
Problemas na minha percepção do cheiro me tornam mais irritado	
Eu como menos fora de casa por causa dos meus problemas com perda de olfato	
Eu como menos que antes (perda de apetite) por causa dos meus problemas com perda de olfato	
Eu tenho que me esforçar mais para relaxar devido aos meus problemas com perda de olfato	
Eu tenho medo de nunca me acostumar com meus problemas com perda de olfato	

Fig. 1 QOD-NS questions, validated for Brazilian Portuguese.

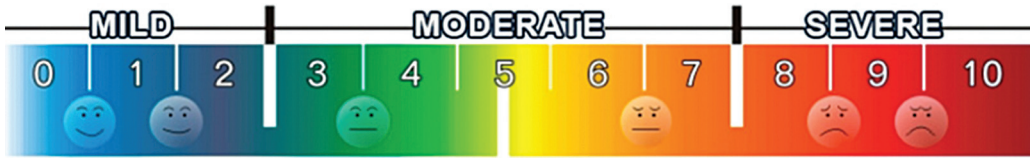


Fig. 2 Visual analogue scale (VAS).

Follow-up of the patients was carried out at 3 and 6 months, with evaluation of complaints, adherence to treatment and visual analogue scale, Alcohol Sniff Test, and Connecticut Olfactory Test scores.

Results

Out of the 1,382 patients contacted, the study included a total of 19, 2 of whom dropped out, leaving 17 patients. The test group had 10 participants and the control group, 7.

Statistical analysis was performed using the R language v. 4.3.1 software (R Foundation for Statistical Computing, Vienna, Austria), parametric t-test for different samples, Friedman's and Mann-Whitney tests.

The baseline characteristics of the participants are shown in ►**Table 1** and were generally well-balanced. The non-parametric t-test showed a statistically significant difference between groups ($p < 0.05$) only in terms of age.

The results at baseline, and at 3 and 6 months are described in ►**Table 2** and ►**Graphs 1–3**. There was no statistically significant difference between groups ($p > 0.05$), according to the non-parametric T-test, for the primary outcome of the variables of interest (visual analogue scale, Alcohol Sniff Test, and Connecticut Olfactory Test).

The improvement of scores over time was assessed by the Friedman's test, which showed statistical significance ($p = 0.0231$) for Alcohol Sniff Test results in same-group analysis.

For categorical variables, the Mann-Whitney test was calculated, and there was no statistically significant difference between groups ($p > 0.05$), in accordance with the numerical evaluation. There was an improvement in the category of smell alteration in 71.5% of patients, and maintenance of the category in 28.5% of patients (►**Graph 4**).

No complications associated with therapy were reported.

Discussion

There was no statistically significant difference to affirm benefit from systemic corticosteroid therapy in persistent postinfectious smell dysfunction ($p > 0.05$). Improvement was observed in both groups, which suggests that olfactory training may be a relevant treatment option.

A search of the literature has shown a few similar articles. Le Bon et al.,[15] in a study with 27 patients, found benefit for use of oral corticosteroids in post-coronavirus disease 2019 (COVID-19) hyposmia ($p = 0.007$), but the olfactory alterations were acute, only 5 weeks after infection. Pendolino et al.,[16] in a 6-month cohort of 44 patients with prolonged hyposmia after COVID-19, did not find superiority of corticosteroids compared to olfactory training. Genetzaki et al.,[5] in a non-randomized trial with 131 participants with non-COVID postinfectious hyposmia, also found no difference between isolated olfactory training and a combination of that with corticosteroids, but the duration of olfactory loss was variable and only described for subgroups of those who used

KIT PARA TESTE OLFATÓRIO

LIMIAR OLFATÓRIO					IDENTIFICAÇÃO DE ODORES				
	Tester	DATA __/__	DATA __/__	DATA __/__		Tester	DATA __/__	DATA __/__	DATA __/__
1	Álcool N-Butílico 200 µL				1	CAFÉ			
2	Álcool N-Butílico 66,6 µL				2	SABONETE			
3	Álcool N-Butílico 22,5 µL				3	CANELA			
4	Álcool N-Butílico 6,6 µL				4	PAÇOCA			
5	Álcool N-Butílico 2,5 µL				5	CHOCOLATE			
6	Álcool N-Butílico 0,83 µL				6	TALCO			
7	Álcool N-Butílico 0,25 µL				7	NAFTALINA			
8	Água Destilada				8	VICK VAPORUB			
	Score					Score			

USO EM CONSULTÓRIO – CONSERVAR EM LOCAL SECO E FRESCO
APÓS ABERTO, VALIDADE DE 3 MESES ou até a validade do kit.

Fig. 3 Connecticut Olfactory Test score sheet, validated for Brazilian Portuguese.

Table 1 Characteristics of participants

Variable	Test group		Control group		*p*-value
	Average	SD	Average	SD	
Gender (M/F)	4/6 (N)	40/60 (%)	3/4 (N)	43/57 (%)	
Age (years)	43.8	10.8	59.4	8.3	0.006
QOD-NS (points)	8	4.7	5.5	7.3	0.3975
Hyposmia time (months)	14	6.6	13.7	6.5	0.9326

Abbreviations: SD, standard deviation; M, male; F, female; QOD-NS, Questionnaire of Olfactory Disorders-Negative Statements.

Table 2 Variables of interest for primary outcome (Visual Analogue Scale, Alcohol Sniff Test and Connecticut Olfactory Test), at baseline, and at the 3- and 6-month follow-ups, comparing test and control groups

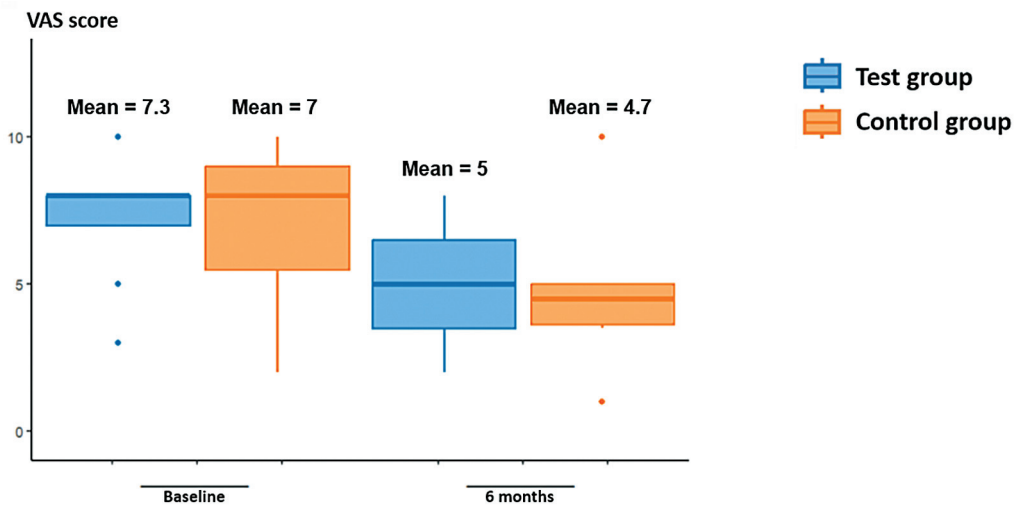
Time	Variable	Test group		Control group		*p*-value
		Average	SD	Average	SD	
Baseline	VAS (points)	7.3	2.2	7	2.8	0.7958
	Alcohol Sniff Test (cm)	15.5	8.4	9.7	12.4	0.2695
	Connecticut (points)	3	1.7	2.3	0.8	0.4012
3 months	VAS (points)	4.4	2.1	6	–	0.4978
	Alcohol Sniff Test (cm)	20.6	6.1	9.7	–	0.1452
	Connecticut (points)	3.5	2.2	4.5	–	0.7075
6 months	VAS (points)	5	2.3	4.7	2.7	0.6254
	Alcohol Sniff Test (cm)	18.8	6.2	13.5	9.3	0.1514
	Connecticut (points)	4.4	1.2	3.3	1	0.7004

Abbreviations: SD, standard deviation; VAS, visual analogue scale; Connecticut, Connecticut Olfactory Test.

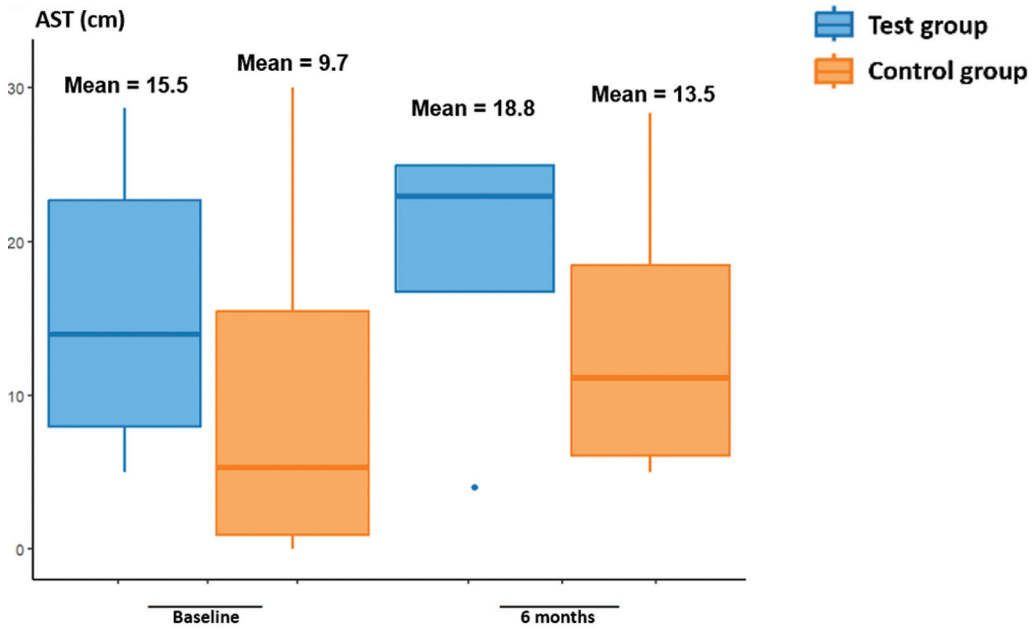
corticosteroids (mean 6.85 ± 1.8 months in improved patients with inflammatory background versus 2.85 ± 1.2 months in improved patients without inflammatory background), suggesting a shorter duration of dysfunction than in our study.

According to the international consensus on olfaction, published in 2022,[6] there is a lack of evidence for the use of corticosteroids in the treatment of smell disorders unrelated to chronic sinusitis or allergic rhinitis. In the absence of these conditions, there are few data to recommend the use of oral corticosteroids.

Olfactory training, first described by Hummel et al., in 2009,[7] is recommended for all types of smell loss, including posttraumatic, postinfectious, idiopathic, and age- or Parkinson's disease-related, and the benefit seems to be greater in postinfectious smell loss. It is a treatment that has no side effects, has proven its safety, and is easy to perform. However, adherence to treatment is a challenge.



Graph 1 Visual analogue scale (VAS) results.

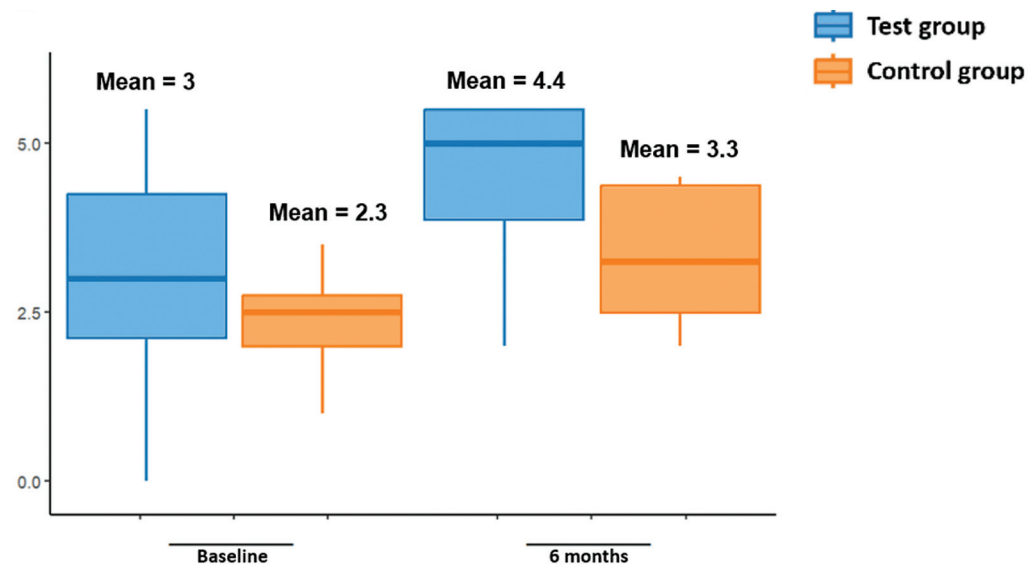


Graph 2 Alcohol Sniff Test (AST) results.

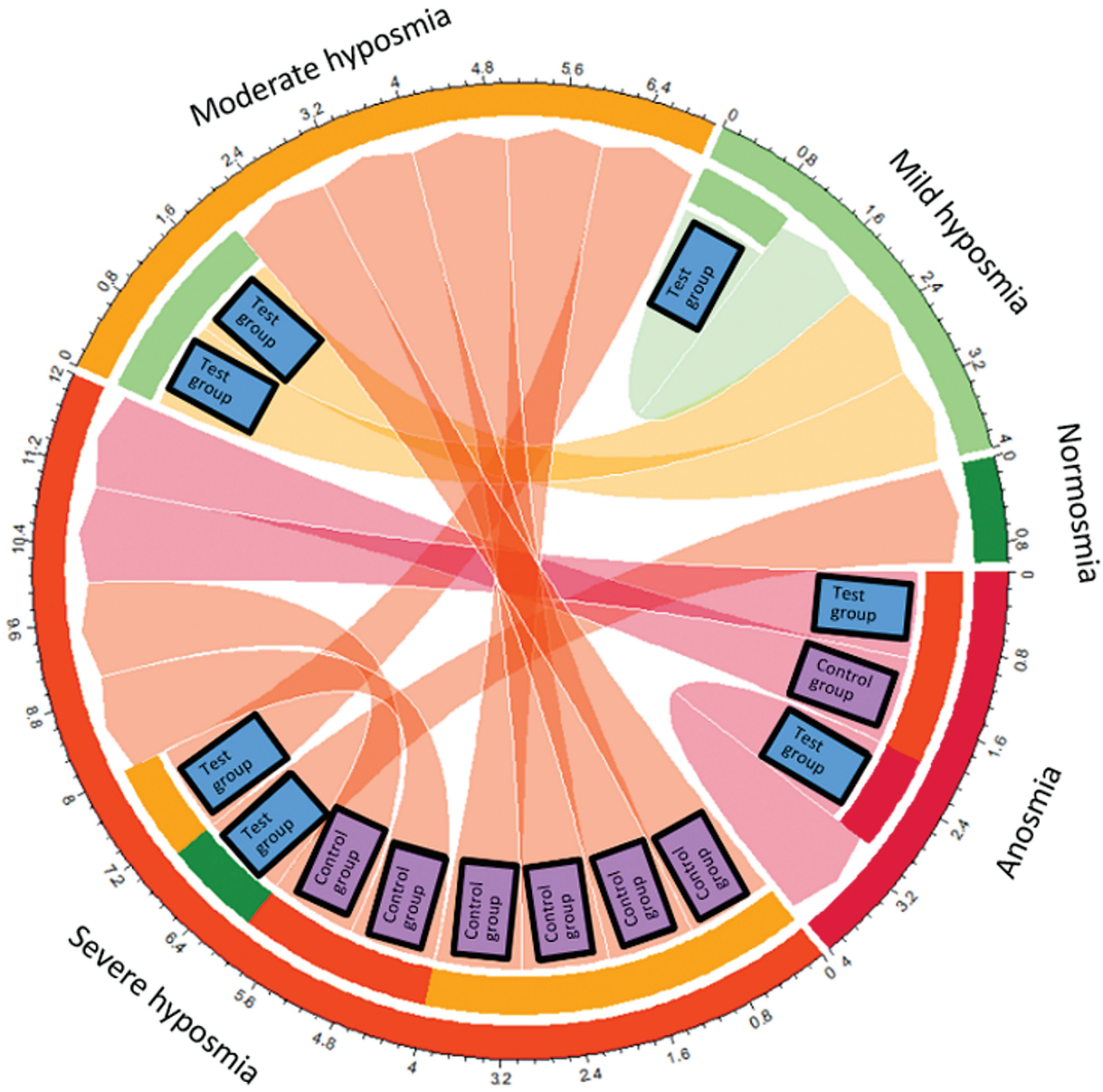
The evaluation of the patients' adherence to olfactory training was performed subjectively over follow-up visits. No breaks in adherence were reported for more than 1 month, usually justified by the lack of perception of improvement. Patients were willing to undergo prolonged treatment after adequate orientation. At the end of the trial, after delivery of objective results, patients expressed satisfaction with scores improvement, which shows how useful objective scores in clinical practice can be, offering evidence of treatment response, given its gradual and prolonged nature, when patient perception is diminished.

Within each group, there was a clear trend of improvement in olfactory function. For disorders with a high rate of spontaneous improvement, demonstrating the benefit of possible treatments is difficult, since the cause of the improvement may be the treatment applied or the natural evolution of the disease itself. However, it would not be ethical to include a control group without any treatment to evaluate improvement over time, in view of the proven benefit of olfactory training for olfactory dysfunction. However, only 3 patients in the test group and 2 patients in the control group had less than 1 year of olfactory loss (respectively 9, 7, and 6 months in the test group and 3 and 9 months in the control group), which reduces the chance of spontaneous improvement, overall, in the study.

The statistical power of the study was reduced by a few factors. Sample size did not achieve the estimated 26 patients



Graph 3 Connecticut Olfactory Test results.



Graph 4 Chord chart of Connecticut Olfactory Test category, from baseline to 6-month follow-up, all participants.

in each group for statistical significance. The two dropouts reported improved olfactory function as a justification for leaving the study.

The groups were not randomized, which could account for a selection bias. However, the current study does not aim to define the theoretical efficacy or safety of systemic corticosteroid therapy. The criteria for dividing the groups are compatible with daily clinical life, considering the profile of comorbidities and the risk-benefit assessment in selecting therapies. There were no reports of side effects from our short-term use of corticosteroids. Even without randomization, the groups were not comparable only in terms of age ($p < 0.05$). This difference, in addition to sample size, may have contributed to the lack of statistical significance between groups.

Conclusion

There was no statistically significant difference to affirm that the use of systemic corticosteroid therapy for patients with persistent smell alteration after an upper airway infection is beneficial ($p > 0.05$). The choice of treatment with systemic corticosteroids should be individualized, and there is still no consensus in the literature.

Olfactory training remains a therapeutical choice for management of postinfectious smell dysfunction.

Funding

The authors declare that they did not receive funding from agencies in the public, private or non-profit sectors to conduct the present study.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Duan HG, Ji F, Yan MX. Treatment of Postinfectious Olfactory Dysfunction Using Corticosteroids. Ear Nose Throat J 2021; 1455613211040368 Epub ahead of print. Doi: 10.1177/01455613211040368

2 Liang F, Wang Y. COVID-19 Anosmia: High Prevalence, Plural Neuropathogenic Mechanisms, and Scarce Neurotropism of SARS-CoV-2? Viruses 2021;13(11):2225. Doi: 10.3390/V13112225

3 Saussez S, Lechien JR, Hopkins C. Anosmia: an evolution of our understanding of its importance in COVID-19 and what questions remain to be answered. Eur Arch Otorhinolaryngol 2021;278(07): 2187–2191. Doi: 10.1007/s00405-020-06285-0

4 de Melo GD, Lazarini F, Levallois S, et al. COVID-19-related anosmia is associated with viral persistence and inflammation in human olfactory epithelium and brain infection in hamsters. Sci Transl Med 2021;13(596):EABF8396. Doi: 10.1126/scitranslmed.abf8396

5 Genetzaki S, Tsakiropoulou E, Nikolaidis V, Markou K, Konstantinidis I. Postinfectious Olfactory Dysfunction: Oral Steroids and Olfactory Training versus Olfactory Training Alone: Is There any Benefit from Steroids? ORL J Otorhinolaryngol Relat Spec 2021;83 (06):387–394. Doi: 10.1159/000516316

6 Patel ZM, Holbrook EH, Turner JH, et al. International consensus statement on allergy and rhinology: Olfaction. Int Forum Allergy Rhinol 2022;12(04):327–680. Doi: 10.1002/alr.22929

7 Hummel T, Rissom K, Reden J, Hähner A, Weidenbecher M, Hüttenbrink KB. Effects of olfactory training in patients with olfactory loss. Laryngoscope 2009;119(03):496–499. Doi: 10.1002/lary.20101

8 Kollndorfer K, Kowalczyk K, Hoche E, et al. Recovery of olfactory function induces neuroplasticity effects in patients with smell loss. Neural Plast 2014;2014:140419. Doi: 10.1155/2014/140419

9 Birte-Antina W, Ilona C, Antje H, Thomas H. Olfactory training with older people. Int J Geriatr Psychiatry 2018;33(01):212–220. Doi: 10.1002/gps.4725

10 Mattos JL, Edwards C, Schlosser RJ, et al. A brief version of the questionnaire of olfactory disorders in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol 2019;9(10):1144–1150. Doi: 10.1002/alr.22392

11 Davidson TM, Murphy C. Rapid clinical evaluation of anosmia. The alcohol sniff test. Arch Otolaryngol Head Neck Surg 1997;123 (06):591–594. Doi: 10.1001/archotol.1997.01900060033005

12 Phenolio GHM, Anselmo-Lima WT, Tomazini GC, et al. Validation of the Connecticut olfactory test (CCCRC) adapted to Brazil. Braz J Otorhinolaryngol 2020;88(05):725–732 S1808-8694(20)30189-0. Doi: 10.1016/j.bjorl.2020.09.013 Epub ahead of print. PMID: 33272838

13 Hura N, Xie DX, Choby GW, et al. Treatment of post-viral olfactory dysfunction: an evidence-based review with recommendations. Int Forum Allergy Rhinol 2020;10(09):1065–1086. Doi: 10.1002/alr.22624

14 Fornazieri MA, Garcia ECD, Lopes NMD, et al. Adherence and Efficacy of Olfactory Training as a Treatment for Persistent Olfactory Loss. Am J Rhinol Allergy 2020;34(02):238–248. Doi: 10.1177/1945892419887895

15 Le Bon SD, Konopnicki D, Pisarski N, Prunier L, Lechien JR, Horoi M. Efficacy and safety of oral corticosteroids and olfactory training in the management of COVID-19-related loss of smell. Eur Arch Otorhinolaryngol 2021;278(08):3113–3117. Doi: 10.1007/S00405-020-06520-8

16 Pendolino AL, Ottaviano G, Nijim J, et al. A multicenter real-life study to determine the efficacy of corticosteroids and olfactory training in improving persistent COVID-19-related olfactory dysfunction. Laryngoscope Investig Otolaryngol 2022;8(01):46–54; Epub ahead of print. Doi: 10.1002/LIO2.989

This preprint was submitted under the following conditions:

- The authors declare that the necessary Terms of Free and Informed Consent of participants or patients in the research were obtained and are described in the manuscript, when applicable.
- The authors declare that the preparation of the manuscript followed the ethical norms of scientific communication.
- The authors declare that they are aware that they are solely responsible for the content of the preprint and that the deposit in SciELO Preprints does not mean any commitment on the part of SciELO, except its preservation and dissemination.
- The authors declare that the data, applications, and other content underlying the manuscript are referenced.
- The deposited manuscript is in PDF format.
- The authors declare that the research that originated the manuscript followed good ethical practices and that the necessary approvals from research ethics committees, when applicable, are described in the manuscript.
- The authors declare that once a manuscript is posted on the SciELO Preprints server, it can only be taken down on request to the SciELO Preprints server Editorial Secretariat, who will post a retraction notice in its place.
- The authors agree that the approved manuscript will be made available under a Creative Commons CC-BY license.
- The submitting author declares that the contributions of all authors and conflict of interest statement are included explicitly and in specific sections of the manuscript.
- The authors declare that the manuscript was not deposited and/or previously made available on another preprint server or published by a journal.
- If the manuscript is being reviewed or being prepared for publishing but not yet published by a journal, the authors declare that they have received authorization from the journal to make this deposit.
- The submitting author declares that all authors of the manuscript agree with the submission to SciELO Preprints.