Budesonide irrigation with olfactory training improves outcomes compared with olfactory training alone in patients with olfactory loss

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Background: **Olfactory training (OT) helps many patients with olfactory loss, but unfortunately it is ineffective for a significant number of patients. Budesonide irrigations are widely used to help patients with paranasal sinus inflammation, but have never been tested as a treatment for olfactory loss. We sought to examine the effect of adding budesonide irrigation to olfactory training on patients with olfactory loss without any visible sign of sinonasal inflammation.**

Methods: **In this randomized, controlled trial, 138 patients with olfactory loss and without any visible sign of sinonasal inflammation were randomized to either OT with saline irrigations or OT with budesonide irrigations. The University of Pennsylvania Smell Identification Test (UPSIT) was administered at the beginning of the study and at 6 months.**

Results: **A total of 133 patients completed the study. Forty-seven patients (35.3%) had a clinically significant change in UPSIT score. Among those in the budesonide irrigation + olfactory therapy group, 43.9% improved, compared with 26.9% in the saline irrigation + olfactory therapy group ($p = 0.039$); this corresponds to an odds ratio of 3.93 (95% confidence interval, 1.20-12.88) in a fully adjusted model ($p = 0.024$). Younger age and shorter duration of olfactory loss were also significant predictors of improvement.**

Conclusion: **Adding budesonide irrigation to olfactory training significantly improved olfactory ability compared with olfactory training plus saline irrigation.** © 2018 ARS-AAOA, LLC.

Key Words:
anosmia; budesonide; hyposmia; inflammation; nasal irrigation; olfaction; olfactory loss; olfactory training

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Olfactory dysfunction effects a surprisingly large segment of the population. Up to 16% of the general population have olfactory dysfunction; 6% are anosmic.[1] By age 50, 25% of adults lose some amount of olfactory function.[1,2] Olfactory loss debilitates people in a variety of ways, such as by preventing detection of hazardous smells (ie, gas leaks, smoke, and chemical vapors); diminishing the enjoyment of food, which can lead to anorexia or weight gain; and inducing psychological distress, such as depression, anhedonia, and social isolation.[2–4] Approximately one third of patients with olfactory dysfunction have symptoms of depression, and a third report severe distress as a consequence of their inability to smell.[3,5]

The most commonly known causes of olfactory dysfunction are acute upper respiratory infections, trauma, and chronic inflammatory sinonasal disease.[2,6] Olfactory loss caused by chronic sinonasal disease is often treatable. However, for a significant subset of patients, olfactory loss is idiopathic without associated paranasal inflammatory disease, or, even when an initial inflammatory insult has created the deficit, any significant sign of mucosal inflammation is gone by the time the patient presents for treatment. For these patients, the pathophysiology of olfactory loss is poorly understood and few treatment options are available. One of the therapies offered is olfactory training, in which patients perform routine and repetitive smelling of specific odors for 12–56 weeks.[2,7] The rationale is that, with repeated exposure to odors, the olfactory neurons could be prompted to regenerate and/or recreate synaptic

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pathways to the olfactory cortex. Numerous studies have demonstrated that olfactory training can improve olfactory function and sensitivity.[2,7] However, this treatment does not help everyone. Across these studies, olfactory training remained ineffective for 50%-85% of study subjects.[8–11]

For these patients, many have hypothesized that olfactory loss may be caused by underlying inflammation within the olfactory epithelium or nerves themselves. Strong evidence suggests that inflammation is highly correlated with olfactory dysfunction, especially in well-known scenarios such as chronic olfactory dysfunction occurring after upper respiratory tract infections, where inflammation permanently damages the olfactory system such that smell loss persists even after the infection has resolved.[6,12] Studies have also identified inflammatory cytokines specifically associated with chronic rhinosinusitis (CRS)–associated olfactory loss.[13–17] Inflammation of the sinonasal mucosa can spread to and damage the adjacent olfactory epithelium, leading to sensory impairment.[17] If subclinical inflammation is a significant contributor to persistent olfactory loss, adding topical steroids that actually have the ability to reach the olfactory cleft could boost the efficacy of olfactory training.

Budesonide is a corticosteroid that has been used to treat many sinonasal diseases, including allergic rhinitis, nasal polyps, and CRS. Budesonide irrigations are widely used in the United States for treating the paranasal sinus inflammation of CRS, with a high safety profile with short-term use.[18] However, there has been no research on the potential use of budesonide specifically for olfactory loss. In this study, we sought to study the effect of budesonide irrigation in addition to olfactory training on patients with olfactory loss without any visible sign of sinonasal inflammation.

Methods

Patients

All patients enrolled in this study were assessed at the Stanford Sinus Center, Department of Otolaryngology–Head and Neck Surgery, Stanford University School of Medicine. A total of 133 patients were included in the study, 41 men and 92 women (average age, 56.3 ± 14.7 years). The study started with 234 patients presenting with the primary complaint of anosmia. Exclusion criteria were: age <18 years; anosmia associated with sinusitis, allergic rhinitis, or sinonasal tumors; peak nasal inspiratory flow (PNIF) ≥50 points under mean established values; or presentation to our clinic at <6 months of onset, to avoid confounding with spontaneous resolution. A total of 138 patients met our eligibility requirements and, of these, 5 were dropped from the study due to loss to follow-up. Based on medical history, olfactory loss was classified as postviral, medication-related, traumatic, environmental exposure, or idiopathic. In all patients, age, gender, race, etiology, history of smoking, and duration of olfactory loss were recorded (Table 1).

Patients were randomized to be treated with olfactory training with saline irrigations (control) or olfactory training with budesonide irrigations. The University of Pennsylvania Smell Identification Test (UPSIT) was used at the beginning of the study and at 6 months to monitor patient progress, with a clinically significant difference considered to be a change in total score of ≥5.[11,19]

TABLE 1. Descriptive characteristics of the study groups

Characteristics	OT + saline irrigation (n = 67)	OT + budesonide irrigation (n = 66)	p^a
Age (years)	56.9 ± 14.7	55.6 ± 14.8	0.59
Gender			0.61
Male	22 (32.8)	19 (28.8)	
Female	45 (67.2)	47 (71.2)	
Race			0.77
White	43 (64.2)	44 (66.7)	
Black	10 (14.9)	9 (13.6)	
Asian	6 (8.9)	3 (4.6)	
Hispanic	8 (11.9)	10 (15.2)	
Smoking			0.32
No	50 (74.6)	54 (81.8)	
Yes	17 (25.4)	12 (18.2)	
Etiology			0.86
Postviral	30 (44.8)	32 (48.5)	
Idiopathic	24 (35.8)	22 (33.3)	
Medication-related	4 (6.0)	2 (3.0)	
Traumatic	7 (10.5)	9 (13.6)	
Environmental exposure	2 (3.0)	1 (1.5)	
Duration of olfactory loss			0.91
<1 year of loss	15 (22.4)	14 (21.2)	
1–2 years of loss	22 (32.8)	24 (36.4)	
>2 years of loss	30 (44.8)	28 (42.4)	

Data expressed as mean ± standard deviation or as number (%).
[a]Calculated using the chi-square test or the Fisher exact test when appropriate.

Olfactory training

Olfactory training was carried out in a twice-daily fashion over a 6-month time period, with 4 specific patient-purchased essential oils, as described in an earlier study.[11]

Nasal irrigations

A NeilMed™ (NeilMed, Santa Rosa, CA) squeeze bottle and salt packets, along with distilled or filtered water, was used to deliver saline irrigations twice a day for 6 months. Budesonide respules in a 0.5-mg/2-mL dose were added to the irrigation bottles of those patients randomized to that arm. In-person demonstration and instruction along

with handouts were provided to these patients. This rinsing, along with the olfactory training, was tracked by journal entry. Calls were made to the patients at the midway mark of the study to ensure and encourage continued compliance.

Statistical analysis

Statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute, Inc, Cary, NC). For continuous variables, a two-tailed *t* test was used. For categorical variables, a chi-square or Fisher exact test was used. The fully adjusted odds ratios (ORs) were calculated using logistic regression analysis, adjusted for age, gender, race, etiology, smoking status, and duration of olfactory loss.

Results

One hundred thirty-eight patients were enrolled, and 133 completed the study. The 2 groups were similar in age, gender, race, etiology, smoking status, and duration of olfactory loss at baseline (Table 1). Forty-seven patients (35.3%) had a clinically significant improvement in olfaction. Nearly double the patients in the budesonide irrigation group (43.9%) improved compared with the control group (26.9%) ($p = 0.039$; Table 2). Younger age and shorter disease duration were also significantly associated with improvement ($p < 0.0001$ for both; Table 2). When fully adjusted for all variables, the OR was 3.93 (95% confidence interval, 1.20-12.88; $p = 0.024$) (Table 3).

Discussion

Budesonide irrigation has been widely used to effectively manage the symptoms of CRS and many other sinonasal diseases. However, its use for olfactory loss has not been described previously. In this study, we found that budesonide irrigation with olfactory training is superior to olfactory training alone in improving olfactory function in patients with anosmia, with a crude OR of 2.13 and a fully adjusted OR of 3.93 (Table 3). It is important to note that, as this was a randomized, controlled trial and the variables between the 2 groups were well balanced (Table 1), a full multivariate adjustment was most likely unnecessary.

Fleiner et al[9] suggested that addition of a corticosteroid to olfactory training could improve olfactory function relative to olfactory training alone. However, their study was nonrandomized and nonblinded, with a relatively small study population of 46 patients. A third of the patients in the study had olfactory dysfunction due to sinonasal etiology, and a third due to postinfectious upper respiratory tract infection (URTI). The authors noted that the olfactory improvement seen in the patients who received adjunctive topical steroids could have been due to the steroids' effect in treating the underlying sinonasal disease. Moreover, the data were collected from patients at 2 different time-points: 4 months and 8 months. Although similar proportions of patients in the olfactory training and olfactory training + steroid groups showed clinically relevant improvement at

TABLE 2. Characteristics of patients in regard to outcome

Characteristics	No clinical significant change (n = 86)	Clinically significant change (n = 47)	p^a
Age (years)	61.5 ± 14.4	46.6 ± 9.5	<0.0001
Gender			0.85
Male	27 (31.4)	14 (29.8)	
Female	59 (68.6)	33 (70.2)	
Race			0.50
Caucasian	57 (66.3)	30 (63.8)	
Black	14 (16.3)	5 (10.6)	
Asian	4 (4.7)	5 (10.6)	
Hispanic	11 (12.8)	7 (14.9)	
Smoking			0.58
No	66 (76.7)	38 (80.9)	
Yes	20 (23.3)	9 (19.1)	
Etiology			0.60
Postviral	42 (48.8)	20 (42.6)	
Idiopathic	31 (36.1)	15 (31.9)	
Medication related	3 (3.5)	3 (6.4)	
Traumatic	8 (9.3)	8 (17.0)	
Environmental exposure	2 (2.3)	1 (2.1)	
Duration of olfactory loss			<0.0001
<1 year of loss	7 (8.1)	22 (46.8)	
1–2 years of loss	29 (33.7)	17 (36.2)	
>2 years of loss	50 (58.1)	8 (17.0)	
Treatment			0.039
Saline irrigation (control)	49 (57.0)	18 (38.3)	
Budesonide irrigation	37 (43.0)	29 (61.7)	

Data expressed as mean ± standard deviation or as number (%).
[a]Calculated using the chi-square test or the Fisher exact test when appropriate.

TABLE 3. Comparison between crude and adjusted ORs for clinically significant change

Crude			Adjusted		
OR	95% CI	p^a	OR	95% CI	p^b
2.13	1.03–4.41	0.039	3.93	1.20–12.88	0.024

[a]Calculated using the chi-square test.
[b]Adjusted for age, gender, race, etiology, smoking status, and duration of olfactory loss using logistic regression analysis.
CI = confidence interval; OR = odds ratio.

4 months (10.7% and 11.1%, respectively), an additional 22.2% of patients in the olfactory training + steroid group improved at the 8-month mark, three fourths of whom were the patients with post-URTI etiology. The authors noted that this improvement in post-URTI patients could have been due to spontaneous resolution of olfactory function after time, which has been reported in the literature. Although their study did suggest that topical steroid application to the nasal cavity in addition to olfactory training could improve olfactory function, it is difficult to determine whether the improvement was from treating underlying inflammation etiology (as for sinonasal disease), spontaneous resolution, or if the steroid therapy provided true additional efficacy in improving olfactory function.

Our study differs from that of Fleiner et al in that we looked at patients with olfactory loss without any sign of paranasal inflammation. This allowed us to be more confident that any olfactory improvement due to steroid irrigation would not be confounded by treating underlying sinonasal disease. Moreover, by including only patients with a history of at least 6 months of anosmia, there was a decreased probability that the olfactory improvement during our study was due to spontaneous resolution.

We hypothesized that, for these patients, although inflammation may not be grossly apparent, their olfactory loss may be caused by underlying microscopic inflammation of the olfactory epithelium or nerves. Studies have shown increased levels of various proinflammatory cytokines or increased activity of inflammatory mediators associated with CRS-associated olfactory loss.[14–17] Furthermore, a study of hyposmic patients showed significantly elevated levels of interleukin-6 (IL-6), a proinflammatory cytokine, in the patients' nasal mucous secretions compared with controls.[13] The exact mechanism for how these cytokines could lead to olfactory dysfunction is not well understood. However, the association of increased levels of inflammatory mediators or their activity suggests that inflammation is likely a key player in olfactory loss. If true, this most likely explains why the addition of budesonide irrigations to treatment improved patient outcomes as seen in our study. Xaubet et al found that budesonide inhibited IL-6 and IL-8 secretions by 49% and 51%, respectively, in cultured nasal mucosal and polyp epithelial cells.[20] A randomized, controlled study of patients with perennial allergic rhinitis also showed that budesonide nasal spray significantly reduced IL-4, IL-5, and IL-6 levels when compared with baseline and placebo.[21] In our study, we speculate that budesonide potentiated the effects of olfactory training by dampening any asymptomatic inflammation that could be causing or exacerbating olfactory loss and preventing appropriate neuronal regeneration. Questions remain whether budesonide irrigation would increase olfactory function without olfactory training and, if so, to what extent.

The mode of delivery of budesonide in an irrigation also most likely contributes to its efficacy. Unlike topical nasal sprays, nasal irrigation can be well distributed throughout the entire nasal cavity. Studies of nasal irrigation techniques using radioisotopes[22] or radiopaque contrast[23] showed that both the anterior and posterior nasal cavity are well irrigated regardless of technique, and the sinuses may be irrigated as well, although not to the same extent. In contrast, nasal sprays are much less effective in covering the entire nasal cavity and are particularly poor at delivery to the posterior or superior nasal cavity.[24] For patients with olfactory loss, steroid irrigation is able to reach the olfactory cleft region to exert its anti-inflammatory effects, making it more effective than topical steroid spray administration.

Limitations of our study include possible differences in patient adherence to olfactory training not noted on journal entry or by patient report, and the inevitable slight differences in how patients may conduct their olfactory training at home. However, we suspect that this would be balanced in the 2 groups by randomization.

Conclusion

Olfactory training with budesonide irrigation significantly improves olfaction compared with olfactory training using saline irrigation alone.

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