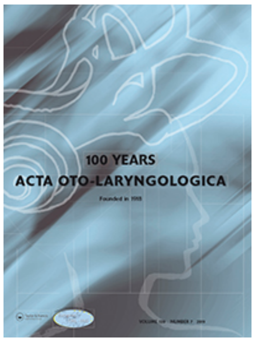

Acta Oto-Laryngologica

ISSN: 0001-6489 (Print) 1651-2251 (Online) Journal homepage: https://www.tandfonline.com/loi/ioto20

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To cite this article: Xiao-Feng Qiao, Guo-Ping Wang, Xin Li, Yin-Huan Bai & Wei Zheng (2019) Analysis of the clinical effect of olfactory training on olfactory dysfunction after upper respiratory tract infection, Acta Oto-Laryngologica, 139:7, 643-646, DOI: 10.1080/00016489.2019.1614224

To link to this article: https://doi.org/10.1080/00016489.2019.1614224

Published online: 24 May 2019.

ACTA OTO-LARYNGOLOGICA
2019, VOL. 139, NO. 7, 643–646
https://doi.org/10.1080/00016489.2019.1614224

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RESEARCH ARTICLE

Analysis of the clinical effect of olfactory training on olfactory dysfunction after upper respiratory tract infection

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ABSTRACT

Background: Olfactory dysfunction is a common symptom during otolaryngology outpatient service.
Objective: To explore the clinical effect of olfactory training on olfactory dysfunction after upper respiratory tract infection (URTI), and its influence factors.
Material and methods: A total of 60 confirmed cases of URTI-induced olfactory dysfunction were enrolled into the present study. The olfactory training lasted for 24 weeks. These patients were tested using Sniffin' Sticks and threshold-discrimination-identification (TDI) composite scoring before treatment, and at 1, 3 and 6 months after treatment.
Results: It was found that URTI-induced olfactory dysfunction patients had more evident deterioration in odor identification ability. The effective rates of olfactory training on olfactory dysfunction at 1, 3 and 6 months after treatment were 1.67%, 26.67% and 41.67%, respectively. The TDI scores at the 3rd and 6th months, but not at the 1st month, were significantly higher, when compared to those before treatment. The course of diseases was a significant influence factor on the therapeutic effect of olfactory training (OR = 0.805, 95% CI: 0.696–0.931).
Conclusions: Olfactory training can efficiently cure URTI-induced olfactory dysfunction, and in particular, significantly improve the odor discrimination ability and odor identification ability.
Significance: Providing useful data for further research regarding olfactory dysfunction.

ARTICLE HISTORY
Received 28 March 2019
Revised 16 April 2019
Accepted 28 April 2019

KEYWORDS
Olfactory dysfunction; olfactory training; upper respiratory tract infection

Introduction

Olfactory dysfunction is a common symptom during otolaryngology outpatient service, and is mainly induced by three causes, including upper respiratory tract infection (URTI), nasal-sinal diseases, and head injuries. In particular, the incidence rate of secondary olfactory dysfunction after URTI is 37.9% [1]. During clinical treatment of secondary olfactory dysfunction after URTI, very few treatment methods are available once the therapeutic effects of drugs are unsatisfactory. The new therapy of olfactory training, in which the recovery of olfactory functions is promoted through periodical and repeated active smelling of diverse odors every day, has attracted wide attention from global experts and researchers, owing to its convenience and effectiveness. Clinical studies have indicated that this training is beneficial for the olfactory functions of olfactory dysfunction patients, but the clinical effects differ [2], suggesting the medical evidences should be expanded and enriched. In the present perspective study, the therapeutic effect and influence factors of olfactory training on post-URTI olfactory dysfunction were investigated.

Material and methods

Clinical data

A total of 68 outpatients with URTI-induced olfactory dysfunction treated in the Department of Otolaryngology at Shanxi People's Hospital between December 2016 and June 2018 were enrolled to the present study. The study was approved by the Ethics Committee of the hospital. All included subjects provided a signed informed consent.

The inclusion criteria were as follows: (1) definite history of URTI and secondary olfactory dysfunction after viral infection, without a blank period between the two, and the course of olfactory dysfunction was $\leq$ 24 months; (2) detailed inquiry of medical history to exclude history of traumas, Alzheimer's disease, Parkinson's disease, mental diseases and immune diseases; (3) nasal endoscopic examination to eliminate nasal neoplasm, nasal sinusitis, allergic rhinitis, olfactory cleft edema and other nasal diseases; (4) sinal computed tomography (CT) and head magnetic resonance imaging (MRI) to exclude space-occupying diseases in the nasal cavity, sinus and intracalvarium, as well as neurodegenerative diseases; (5) uncured by the medication of

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glucocorticoids, gingko extracts, or vitamin A, and the time of drug therapy was >1 month.

Exclusion criteria were as follows: contraindication to the therapeutic method or drugs; interruption due to non-endurance or adverse reactions during the therapy; development of other diseases or need of other drugs that might interfere with the therapeutic effects.

Methods

Medical data collection

Information was collected from all included patients through questionnaire investigation, including gender, age, body mass index (BMI), course of disease, history of smoking/drinking, history of diabetes, history of hypertension, presence of taste dysfunction, and the visual analog scale (VAS) score.

Olfactory function test

Sniffin' Sticks (Burghart, Germany) were used in the tests before treatment, and at 1, 3 and 6 months after treatment. These tests included three parts: (1) Odor threshold test: A total of 48 pen-like sticks were equally divided into 16 groups. Each group involved two blank control sticks and one n-butanol solution stick. The highest score was 16 (the lowest concentration can be discriminated), while the smallest score was 0 (the highest concentration cannot be discriminated). (2) Odor discrimination test: A total of 48 new pen-like sticks were equally divided into 16 groups. Each group contained two solutions of the same smell reagent, and one solution of a different smell reagent. If all groups could be discriminated, the score was 16. (3) Odor identification test: A total of 16 pen-like sticks were involved. After the subject smelled one stick, the subject should choose one from the four provided answers. If all choices were correct, the score was 16. After these three tests, the scores of odor threshold (T), odor discrimination (D) and odor identification (I) were added together. The result would be the threshold-discrimination-identification (TDI) score used to evaluate the olfactory function.

Therapeutic regimen

Four reagents with different odors were used, including benzene ethanol (rose), menthol (mint), citronellal (lemon), and eugenol (clove) (all 100%, from Sigma-Aldirch, USA). Each odorant was smelled for 10 s/time, and the interval between two odorants was 10 s. Each olfactory training session lasted for five minutes, and the training frequency was one time before breakfast and one time before sleep everyday [3]. The olfactory function was tested at 1, 3 and 6 months after treatment.

Therapeutic effect assessment

The therapeutic effect was assessed according to the variation of mean TDI scores after treatment, and a change of >6 was considered "effective" [4].

Statistical methods

The statistical analysis was performed using SPSS 20. With the clinical effect as the dependent variable, logistic regression analyses were performed with the independent variables of gender, age, BMI, course of disease, history of smoking/drinking, history of diabetes, history of hypertension, presence of taste dysfunction, VAS score, and preoperative TDI score. The TDI scores before and after treatment were compared *via* paired *t*-test.

Results

Basic information

Eight of the 68 included cases were excluded due to interruption or missed follow-up, which led to the enrollment of 60 cases for the therapeutic effect observation. These 60 patients, which comprised of 20 males and 40 females, were within 25–65 years old (52.4 ± 12.3 years old). The course of disease lasted within 6–21 months (13.4 ± 4.8 months). A BMI of ≥ 24 was found in 22 patients (36.7%). The number of patients with a history of drinking, diabetes, hypertension and taste dysfunction were 11 (18.3%), 14 (23.3%), 17 (28.3%), and 19 (31.7%), respectively. The VAS score was 4.13 ± 1.87. In terms of age and gender, the included patients were mostly old women (66.7% females), and this was consistent with another study, in which the URTI-induced olfactory dysfunction mostly attacked women who were above the age of 50 years old [5]. The olfactory dysfunction was dominated by hyposmia (43 cases) and anosmia (17 cases). The TDI scores were dominated by the deterioration of olfactory identification ability.

Clinical efficacy

The effective rates of olfactory training on URTI-induced olfactory dysfunction at 1, 3 and 6 months after treatment were 1.67%, 26.67% and 41.67%, respectively. The TDI scores at the 1st month were not significantly different, when compared to those before treatment ($p > .05$). The scores at the 3rd and 6th months were both significantly higher, when compared to those before treatment ($p < .05$). The odor discrimination ability and odor identification ability both improved at the 3rd and 6th month after treatment (all, $p < .05$), but the odor threshold did not significantly increase (both, $p > .05$; Table 1).

Influence factors on the clinical effect

The single-factor logistic analysis revealed that the course of diseases was significantly correlated with the therapeutic effect. Patients with a shorter course of disease (time duration from the first onset of symptoms to the start of olfactory training) had a significantly better therapeutic effect (OR = 0.805, CI: 0.696–0.931, $p = .004$; Table 2).

Table 1. The TDI scores before and after treatment.

Time	T	D	I	TDI
Before treatment[a]	6.76 ± 1.96	7.17 ± 1.74	2.88 ± 1.51	16.82 ± 2.67
1 month after treatment[b]	6.88 ± 2.15	7.32 ± 1.85	2.75 ± 1.67	17.30 ± 2.96
3 months after treatment[c]	6.91 ± 2.03	8.70 ± 1.96	4.92 ± 1.71	20.53 ± 3.01
6 months after treatment[d]	6.86 ± 2.35	9.48 ± 2.18	6.13 ± 1.62	22.48 ± 3.73
$T^{a\text{-}b}$ (P)	−1.121 ($p > .05$)	−1.454 $p > .05$	0.893 $p > .05$	−1.819 $p > .05$
$T^{a\text{-}c}$ (P)	−1.501 ($p > .05$)	−12.091 ($p < .05$)	−11.047 ($p < .05$)	−11.065 ($p < .05$)
$T^{a\text{-}d}$ (P)	−0.799 ($p > .05$)	−16.134 ($p < .05$)	−17.561 ($p < .05$)	−15.400 ($p < .05$)
$T^{b\text{-}c}$ (P)	−0.333 ($p > .05$)	−10.609 ($p < .05$)	−13.716 ($p < .05$)	−10.893 ($p < .05$)
$T^{b\text{-}d}$ (P)	0.063 ($p > .05$)	−14.755 ($p < .05$)	−20.112 ($p < .05$)	−13.257 ($p < .05$)
$T^{c\text{-}d}$ (P)	0.375 ($p > .05$)	−7.176 ($p < .05$)	−8.045 ($p < .05$)	−6.765 ($p < .05$)

TDI: threshold-discrimination-identification; a: before treatment; b: 1 month after treatment; c: 3 months after treatment; d: 6 months after treatment.

Table 2. Regression analysis of influence factors correlated with the clinical effect.

Influence factor	OR	95%CI	*p*
Gender	0.572	0.142–2.306	.432
Age	0.979	0.927–1.033	.435
BMI	1.954	0.545–7.010	.304
Course of disease	0.805	0.696–0.931	.004
History of smoking and drinking	2.558	0.448–14.601	.290
Complicated with taste dysfunction	1.795	0.462–6.979	.399
VAS score	0.988	0.702–1.389	.943
Diabetes	2.821	0.601–13.237	.188
Hypertension	1.492	0.356–6.258	.584
Preoperative TDI	1.061	0.825–1.364	.644

TDI: threshold-discrimination-identification

Discussion

Olfaction is the sensing of odors, and plays critical roles in social communication and the daily life of humans. Olfactory dysfunction impacts quality of life, social communication and nutrient ingestion, and even causes depression or other mental problems [6,7]. One of the common causes of olfactory dysfunction is upper respiratory tract viral infection (URTI). The possible infection mechanism may be correlated with the following: the reduction in the number of olfactory receptors and olfactory fibers, and the loss of olfactory receptor cilium due to viral infection; the replacement of the olfactory epithelia by respiratory epithelia, or massive scaring; olfactory pathway invasion into the olfactory center caused by viral neurotropics. As reported, URTI-induced olfactory dysfunction is dominated by hyposmia, and mainly attacks women with an age of above 50 years old. This may be accompanied with taste dysfunction, but not with other nasal symptoms. The Sniffin' Sticks test mostly revealed the deterioration of the olfactory identification ability, which was more significant. The present study shows that patients are dominated by females (66.7%), who are 52.4 ± 12.3 years old. The olfaction psychophysics tests revealed that olfactory dysfunction was dominated by hyposmia (43 cases, 71.7%). The TDI scores revealed the deterioration of the odor identification ability was more evident. These results are consistent with previous researches. In clinical practice, the preferential medication of URTI-induced olfactory dysfunction is glucocorticoids, ginkgo extracts, and vitamin A. Once the therapeutic effect of drugs is unsatisfactory, the subsequent treatment would be very challenging.

In the novel treatment of olfactory training, the olfaction of the olfactory dysfunction patient is periodically irritated by odorants to recover the olfactory function. The review of relevant studies revealed that olfactory training may be a new and effective intervention for olfactory dysfunction patients, and its effective rate is 28–63% [8]. The olfactory system of mammalians can be regenerated during the whole life, and olfactory epithelia and olfactory bulbs both have strong regeneration ability [9]. The higher olfactory center also has moderate regenerability, which theoretically underlies the treatment of olfactory dysfunction by olfactory training. A recent research revealed that recurrent olfactory irritation can intensify the potential reaction of olfactory epithelia, indicating that olfactory training is involved in olfactory epithelial reconstruction probably by increasing the number of olfactory neurons in humans [10]. In addition to the above direct participation, olfactory training can also significantly enlarge the volumes of olfactory bulbs [11] and improve the network connection of the olfaction-related cerebral cortex [12,13], indicating that olfactory training is critical in regenerating the central nervous system.

The present subjects were URTI-induced olfactory dysfunction patients who had not been cured by drugs. Since unpleasant odors *vs.* pleasant odors can more significantly affect the breathing mode of humans [14] and reduce the work memory ability of a part of normal people [15], four relatively pleasant smells were selected for the present olfactory training. The effective rates of the olfactory training on URTI-induced olfactory dysfunction at 1, 3 and 6 months after treatment were 1.67%, 26.67% and 41.67%, respectively. The TDI scores at the 3rd and 6th months, but not at the 1st month, were significantly higher, when compared to those before treatment. If the relatively long period of olfactory system regeneration was considered, these results can be better explained. The potential influence factors on the clinical effect were investigated *via* Logistic regression analysis, and it was revealed that the major influence factor on prognosis was the course of diseases, which is consistent with previous researches. Both the odor discrimination ability and odor identification ability were significantly improved after 3 and 6 months of training, but the odor threshold did not obviously improve. In other words, the increment of TDI scores in URTI-induced olfactory dysfunction patients after the olfactory training was mainly reflected in the change in odor discrimination ability and odor identification ability, but not in the odor threshold. To date, most studies have held that the olfactory threshold mediates at the olfactory epithelium level, but a functional MRI research has confirmed that olfactory training may lead to the most obvious change in the cortex [12]. Since patients with complete anosmia are nonresponsive to olfactory irritation, it is impossible to use odor excitement to activate the olfactory functions of the olfactory epithelia and the brain. The olfactory system is closely correlated to the nasal trigeminal nerve system, and the majority of odors not only irritates the smell neurons, but also activates the trigeminal nervous system [16,17]. Moreover, the nasal trigeminal nervous system is largely involved in olfactory signal processing, such as odor laterality identification and odor intensity assisted identification [17–19]. Thus, olfactory training can improve the odor discrimination ability and odor identification ability of olfactory dysfunction patients, and the investigators consider that this may be correlated to the deep participation of the nasal trigeminal nervous system. Nevertheless, this idea should be confirmed through further research.

In summary, olfactory training is an effective intervention for patients with URTI-induced olfactory dysfunction, which more significantly improves the odor discrimination ability and odor identification ability. Prolonging and the earlier start of olfactory training would help with the recovery of olfactory functions. In the future, personalized olfactory training would be further explored, such as the time duration of treatment, types of odorants, the nasal trigeminal system, and taste neural function training.

Disclosure statement

The authors declared that they have no conflict of interest.

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