

Intranasal vitamin A is beneficial in post-infectious olfactory loss

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Abstract Vitamin A plays a decisive role in the regeneration of olfactory receptor neurons. In this retrospective study we investigated the effectiveness of topical vitamin A in patients with post-infectious and posttraumatic smell disorders. Retrospective cohort. A total of 170 patients (age range 18–70 years, mean age 52 years) participated. Forty-six patients were treated with smell training only. The remaining 124 patients received smell training and topical vitamin A. Olfactory function was assessed using the Sniffin' Sticks test kit, a validated technique to measure odor thresholds, discrimination and identification. The duration of olfactory training was 12 weeks. In patients receiving vitamin A, this was applied topically (head back position) at a dose of 10,000 IU/day for 8 weeks. Follow-up testing was performed approximately 10 months after the first assessment. Thirty-seven per cent of all post-infectious patients treated with vitamin A exhibited clinical improvement, whereas only 23% improved in controls. Using a Chi-square test, this was a significant result ($\chi^2 = 7.06$, $df = 2$, $p = 0.03$). In addition, when comparing change in score after treatment, olfactory training + vitamin A produced significantly greater improvement compared with training alone, in discrimination score for all patients (1.4 points, $p = 0.008$), and in threshold and discrimination in the post-infectious group

(1.6 points, $p = 0.01$ and 1.4 points, $p = 0.04$, respectively). Intranasal vitamin A at a dose of 10,000 IU per day for 2 months may be useful in the treatment of post-infectious olfactory loss. Further work with prospective, placebo-controlled studies is required to confirm these findings.

Keywords Olfaction · Hyposmia · Vitamin A · Retinoic acid · Therapy · Therapeutics · Drug therapy · Nose

Introduction

Olfactory dysfunction is common and estimated to affect approximately 21.6% of the general population [1], with prevalence rising to almost two-thirds of those over 80 years [2]. While this form of sensory impairment has traditionally received little attention from research or clinical communities, there is increasing evidence that it can negatively impact on quality of life. Associated disease burden results from social and environmental anxiety, reduced food and drink enjoyment, nutritional disturbances and depression [3, 4]. Despite this, effective treatment strategies for olfactory dysfunction are limited.

Olfactory receptor neurons (ORN) are found within the neuroepithelium of the olfactory cleft, where they extend dendritic cilia to the surface mucous layer for odorant binding. Given that ORN are, therefore, directly exposed to the external environment, they are prone to damage through contact with exogenous factors such as toxins, dusts or pathogens. Consequent damage can lead to their degeneration within the neuroepithelium [5], with upstream changes in olfactory bulb volume caused by reduced afferent input [6, 7]. To counteract this damage and maintain function throughout life, the olfactory system has

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a unique capacity to regenerate [8]. In adults regeneration of mature neurons from multipotent precursor (stem) cells is limited to the olfactory neuroepithelium (OE), which produces new ORN, possibly the subventricular zone, which produces interneurons for the OB, and the subgranular zone, where new granule cells are supplied to the dentate gyrus of the hippocampus [9]. Where regeneration of ORN or OB interneurons fails, either through normal aging or other pathophysiological processes, this leads to clinical olfactory dysfunction.

While the mechanism for and degree of regeneration at both the level of the OE and OB in humans is not entirely clear, it is known that certain signaling pathways are required. Retinoic acid (RA), which is a metabolite of vitamin A and a member of the steroid/thyroid hormone superfamily, is a transcription regulator important in tissue development and regeneration [10]. RA signaling has been implicated during olfactory system embryogenesis and adult neuronal regeneration [11].

Given this role, previous studies have investigated the utility of vitamin A in the treatment of olfactory dysfunction, with varying results. The first of these, a case series reported by Duncan and Briggs, reported beneficial effect with high-dose systemic therapy [12]. More recently; however, no significant improvement in olfactory test scores following treatment with oral vitamin A was demonstrated during a double-blind placebo-controlled trial [13].

As the literature base supporting the role of RA signaling in the regeneration and maintenance of the olfactory system is robust, we theorized that treatment with vitamin A may be beneficial, but at higher doses than were used in our previous controlled trial. To circumvent the potential side effects of high-dose systemic therapy, we proposed that vitamin A could be administered topically. Intranasal application in this way should theoretically produce higher localized concentrations at the level of the OE than would be seen with the equivalent dose of systemic therapy.

As the most widely accepted treatment modality for non-sinonasal dysfunction [14–16], olfactory training is presently a standard of care in our center. We, therefore, report the results of a retrospective cohort analysis of patients treated with olfactory training alone, or olfactory training plus intranasal vitamin A at our tertiary referral smell and taste clinic.

Materials and methods

Patient selection

We performed a retrospective cohort analysis based on an audit of patients treated for olfactory dysfunction at our

tertiary referral center. Patients with post-infectious and posttraumatic olfactory dysfunction were included in the study, while those with impairment due to sinonasal disease, neurodegeneration, congenital anosmia or other causes were excluded. Only patients over the age of 18 were included in the study.

Clinical and olfactory assessment

Following a structured history and full ENT examination, all patients underwent olfactory testing using the “Sniffin’ Sticks” test battery (Burghart Messtechnik, Wedel, Germany) [17]. This psychophysical tool allows for the separate assessment of odor threshold (T), discrimination (D) and identification (I), and has been validated in the German population [18]. The results of individual sub-component testing is suggested to differentially reflect underlying pathology (with threshold best reflecting peripheral disease and discrimination/identification cognitive or central disease) [19, 20] while use of a composite ‘TDI’ score increases diagnostic sensitivity [17, 20].

Odor threshold is tested using a 16-step three-alternate forced choice staircase paradigm. During testing, the patient is required to identify which of three randomly presented odor ‘pens’ contains the target odorant [phenylethylalcohol (rose) in odorless propylene glycol diluent] as compared to blank (propylene glycol alone). Pens of increasing concentration (from weakest to strongest: 16–1) are presented until the patient is able to correctly identify the target pen twice in a row. Subsequently, the staircase is reversed and pens of increasingly dilute concentration are presented. When one incorrect answer is encountered, the staircase is once again reversed and this process is continued until seven reversals have been made. The odor threshold is then calculated as the mean of the last four staircase reversal points. The patient is blindfolded during this procedure, and higher scores indicate better olfactory function. Odor discrimination is also a 16 step three-alternative forced choice paradigm. During testing, the patient is presented with three suprathreshold odors and asked to identify which of the three differs from the other two. Again, the patient is blindfolded and higher scores indicate better function. Odor identification is a 16 step four-alternative forced choice paradigm whereby the patient is asked to identify which of four written/visual cues correspond with the presented suprathreshold odor. Higher scores indicate better function.

Differentiation between normosmia, hyposmia and functional anosmia was determined using the following TDI scores [18]:

- Normosmia: ≥ 30.3
- Hyposmia: $>16.5, <30.3$

- Functional anosmia: ≤ 16.5

Clinical improvement has been shown in previous studies to correlate with improvements in TDI score of 5.5 points or greater [21]. While using composite TDI scores is a more sensitive measure of relevant change, clinical improvement can also be assumed where individual scores improve by ≥ 2.5 points for threshold, or by ≥ 3 points for discrimination or identification [21]. Full TDI scores were recorded before and after treatment, as described below.

Treatment

Given the associated literature base, olfactory training is a standard of care in our center [14–16]. All patients were, therefore, treated with olfactory training using four standard odorants [phenylethylalcohol (rose), eucalyptol (eucalyptus), citronellal (lemon), and eugenol (cloves)] for 12 weeks, as has been previously described [14].

In addition to smell training, some patients were also treated with topical vitamin A. Patients were pseudo-randomly chosen to undergo such treatment. Vitamin A (Vitaminol[®], Aristo Pharma GmbH, Berlin, Germany) was administered intranasally at a dose of 10,000 IU once daily, for 8 weeks. While a 12-week period is known to be effective and is, therefore, standard in olfactory training, the ideal duration of treatment with intranasal vitamin A is unknown. Accordingly, 12 weeks of such treatment was deemed to be too long, and patients were treated for 8 weeks only. Patients were instructed to instill the vitamin A drops using a lying position with the head tilted back, which has been suggested to improve access to the upper nasal cavity [22].

Patients were not receiving any other medications or treatments for olfactory dysfunction during this time, and treatment was not commenced until a sufficient washout period had been observed, typically 4 weeks.

Statistical analysis

Statistical analysis was undertaken using SPSS (Version 23, Chicago, IL, USA) and GraphPad Prism (version 6, GraphPad Software, LaJolla California, USA). Significance was assumed where $p < 0.05$. The student's *t* and Chi-squared tests were used wherever appropriate.

Ethical considerations

This study was based on information from a retrospective audit of patient care at our clinic. This approach was approved by our Ethical Committee (EK60032013).

Results

Demographics

Results were obtained from 170 patients who were treated in our center between 2012 and 2015. One hundred and two patients had post-infectious olfactory dysfunction and the remaining patients had posttraumatic loss. Demographic details according to treatment group are shown in Table 1.

In total, 46 patients received only smell training, while the remaining 124 received smell training and topical vitamin A treatment. Post-treatment olfactory testing was undertaken at approximately 10 months. Results from any later olfactory testing were not available.

Mean pre- and post-treatment olfactory scores according to etiology and treatment regimen are shown in Table 2.

For all patients, change in olfactory scores following treatment with training or training + vitamin A are shown in Fig. 1. Treatment groups were then compared using a student's *t* test. In this way, any differences in pre-treatment olfactory scores were controlled for. For all patients, the change in odor discrimination score was significantly greater in the training + vitamin A group compared with the training alone group (1.4 points, $p = 0.008$). Furthermore, there was a trend towards improved odor threshold and composite TDI scores (0.8 points, $p = 0.057$ and 1.5 points, $p = 0.091$, respectively). However, none of these improvements reached clinical significance at the group level (where clinical improvement is assumed if changes in score: TDI ≥ 5.5 , T 2.5, I ≥ 3 , D ≥ 3).

Change in olfactory scores following treatment with training or training + vitamin A according to etiological subgroup are shown in Fig. 2. In the post-infectious group, training + vitamin A produced significantly greater improvement in threshold and discrimination scores than training alone, though again this did not reach clinical significance (1.6 points, $p = 0.01$ and 1.4 points, $p = 0.04$, respectively). There were no other significant differences between the training and training + vitamin A groups.

Looking at individual patient scores, within the post-infectious group, olfactory function improved clinically (as defined by an increase in TDI of ≥ 5.5 points) in 23% of patients who received olfactory training alone. In those who received vitamin A in addition to olfactory training, 37% of patients improved. The proportion of patients who improved with additional vitamin A was statistically significantly higher than the training alone group ($\chi^2 = 7.06$, $df = 2$, $p = 0.03$).

In the posttraumatic group, the proportion of patients who improved with vitamin A was not significantly greater than with training alone ($\chi^2 = 2.48$, $df = 2$, $p = 0.29$).

Table 1 Patient demographics according to etiology

| | All patients | Olfactory training | Olfactory training + vitamin A |
|---|--------------|--------------------|--------------------------------|
| Number | 170 | 46 | 124 |
| Etiology | | | |
| Post-infectious | 102 | 26 | 76 |
| Posttraumatic | 68 | 20 | 48 |
| Age (in years: mean; SD) | 55; 14 | 54; 14 | 55; 14 |
| Duration of disorder (at 1st visit in months: mean; SD) | 14; 37 | 12; 10 | 11; 16 |
| Sex (F:M) | 100:70 | 23:23 | 77:47 |

Table 2 Mean and SD (mean; SD) of pre- and post-treatment TDI scores according to etiology and treatment regimen

| | Pre-treatment | | | Post-treatment | | |
|-------------------------------|---------------|-----------------|---------------|----------------|-----------------|---------------|
| | All patients | Post-infectious | Posttraumatic | All patients | Post-infectious | Posttraumatic |
| Training alone (<i>n</i>) | 46 | 26 | 20 | 46 | 26 | 20 |
| Composite 'TDI' | 18.5; 7.7 | 22.5; 7.1 | 13.2; 4.6 | 20.7; 8.6 | 25.0; 6.6 | 15.2; 7.9 |
| Threshold (T) | 3.5; 2.8 | 4.5; 3.0 | 2.3; 2.1 | 4.0; 3.0 | 4.6; 2.5 | 3.2; 3.5 |
| Discrimination (D) | 8.2; 2.7 | 9.7; 2.5 | 6.4; 1.7 | 8.2; 3.4 | 9.5; 2.9 | 6.5; 3.3 |
| Identification (I) | 7.0; 3.7 | 9.0; 3.4 | 4.5; 2.2 | 8.5; 3.9 | 10.9; 2.7 | 5.5; 2.9 |
| Training + vit A (<i>n</i>) | 124 | 76 | 48 | 124 | 76 | 48 |
| Composite 'TDI' | 17.4; 6.6 | 19.4; 6.0 | 14.3; 6.2 | 21.3; 7.0 | 23.6; 6.1 | 17.6; 6.8 |
| Threshold (T) | 2.5; 2.0 | 2.7; 1.9 | 2.1; 2.1 | 3.8; 2.8 | 4.3; 2.8 | 3.0; 2.7 |
| Discrimination (D) | 8.2; 3.0 | 9.3; 2.5 | 6.6; 3.0 | 9.6; 3.0 | 10.5; 2.4 | 8.1; 3.3 |
| Identification (I) | 6.8; 3.2 | 7.6; 3.2 | 5.6; 2.8 | 7.9; 3.0 | 8.7; 2.9 | 6.5; 2.7 |

Discussion

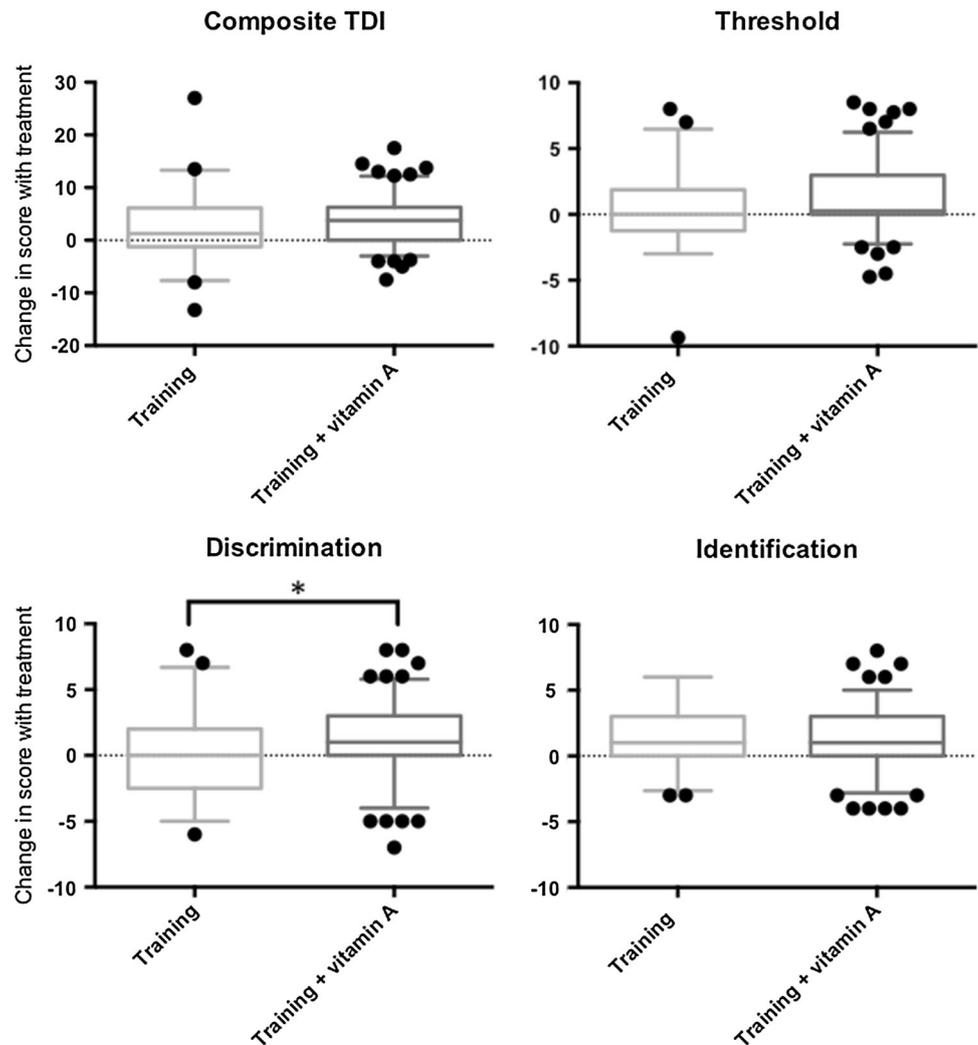
We have demonstrated that topical application of vitamin A in addition to olfactory training may be of benefit in the treatment of post-infectious olfactory loss. However, these results should be interpreted with caution, given that this was a retrospective cohort analysis. Accordingly, we were unable to control for differences between the training + vitamin A group compared with the training alone group. Such differences may potentially have confounded our results. Therefore, to confirm whether vitamin A is beneficial in post-infectious olfactory loss, further prospective, placebo-controlled studies are required. Future studies should also aim to determine whether vitamin A is beneficial in isolation or only in combination with olfactory training.

Infections of the upper respiratory tract are a common cause of olfactory dysfunction. Accordingly, post-infectious olfactory loss is one of the most frequent underlying etiologies presenting to specialist clinics [23, 24]. While a variety of pathogens have been linked with olfactory impairment (including bacteria, fungi, and microfilaria), viral infections are the most common cause [25]. The

underlying pathophysiology is thought to involve damage to the neuroepithelium and possibly central lesions (through transmission of pathogens intracerebrally via the olfactory nerve) [25]. Jafek and colleagues describe histological evidence for the former [5]. Biopsies obtained from patients with post-viral impairment show patchy 'checker-board' distribution of OE, interspersed with respiratory epithelium. Within the residual OE, there is marked disorganization with reduced numbers of ORN. Where ORN are present, they are often shrunken in size with dendrites that do not reach the mucosal surface. Yamagishi and colleagues demonstrated cases of post-infectious olfactory loss in which the OE had been replaced with metaplastic squamous epithelium. Furthermore, they additionally noted that olfactory recovery rate correlated with the number of olfactory receptor cells and intact nerve bundles [26]. Taken together, one may speculate that these results reflect failure of ORN regeneration following viral insult.

The role of RA signaling in the olfactory system has been well documented experimentally. Early work from Anchan and colleagues demonstrated that disruption of RA signaling during mid-gestation leads to disrupted olfactory

Fig. 1 Change in odor scores after treatment for all patients. Error bars represent 95% confidence interval. Significant results are marked with *. Please note the difference in y-axis scales between TDI and threshold/discrimination/identification



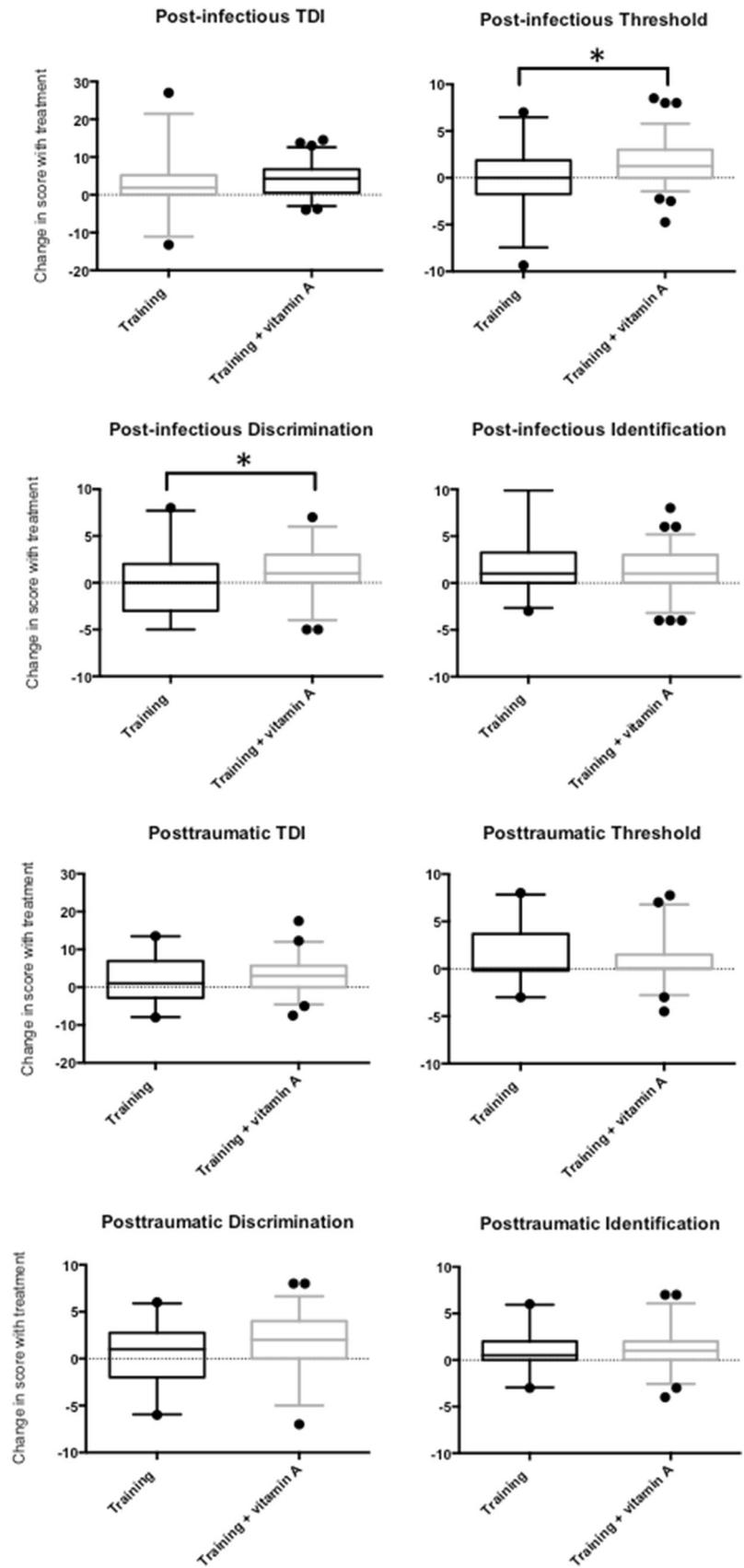
embryogenesis in mice [27]. Further work has demonstrated that RA receptors are present in the adult murine OE, and that these tissues are actively engaged in the synthesis of RA [28]. Due to the localization of RA-activated cells in adult animals (e.g., in the basal OE), in addition to their characteristics when isolated in vitro, it has been argued that such cells represent multipotent olfactory stem cells (reviewed in [11]). Accordingly, RA has been shown in vitro to enhance ORN axonal outgrowth [29], with deficiency leading to increased proliferation of OE basal cell populations and reduced olfactory marker protein (a marker for mature ORN) mRNA [30], and inhibition of RA receptors leading to ORN cell death [31]. Moreover, administration of RA has been shown to enhance olfactory recovery in mice following olfactory nerve transection [32].

Given that failed ORN regeneration is implicated in post-infectious olfactory dysfunction, the above experimental work supports our present findings. As briefly mentioned in the introduction, the utility of vitamin A in

olfactory impairment has also been anecdotally demonstrated by Duncan and Briggs [12]. In their 1962 case series, they describe subjective improvement following varying doses of systemic vitamin A, in 56 patients with olfactory dysfunction of mixed cause. However, the validity of their results is questionable for several reasons. First, they utilized subjective patient reporting to assess olfactory function, which is now known to be unreliable [33]. Second, their protocol was not fixed and patients were treated with varying doses of oral or parenteral vitamin A. Finally, very high doses were used (up to 150,000 IU/day, orally), therefore, substantially increasing the risk of side effects from such treatment.

In an attempt to better delineate the effects of oral vitamin A, Reden et al. performed a double-blind placebo-controlled trial, in which no benefit was seen (according to “Sniffin’ Sticks” scores) following treatment with 10,000 IU, given daily for 3 months [13]. We would suggest that the benefit seen in our present cohort is due to increased local concentration of vitamin A at the OE, when

Fig. 2 Change in odor scores after treatment according to etiological subgroup. *Error bars* represent 95% confidence interval. Significant results are marked with *. Please note the difference in y-axis scales between TDI and threshold/discrimination/identification.



administered intranasally, or possibly due to the combination of topical vitamin A therapy with olfactory training.

As mentioned above, to further delineate the utility of topical vitamin A in post-infectious olfactory dysfunction, we suggest that further studies should be undertaken, using a prospective, double-blind, placebo-controlled design.

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Compliance with ethical standards

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Conflict of interest The author(s) declare that they have no competing interests.

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