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The Role of Olfactory Training and Intranasal Corticosteroid to Improve Olfactory Function in Patients with Olfactory Disorder in Makassar

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KEYWORDS

Olfactory Disorder, Olfactory Training, Intranasal Corticosteroids, Sniffin Stick Test

ABSTRACT:

Introduction: Olfactory disorders can cause a person to lose the ability to detect odors and have been shown to have a poor impact on the patient's quality of life. To date, there are no effective pharmacotherapies to improve olfactory impairment, but olfactory training (OT) for 12 weeks may be an option as a treatment strategy for olfactory impairment due to viral infection.

Objectives Olfactory disorders can cause a person to lose the ability to detect odors and have been shown to have a poor impact on the patient's quality of life. To date, there are no effective pharmacotherapies to improve olfactory impairment, but olfactory training (OT) for 12 weeks may be an option as a treatment strategy for olfactory impairment due to viral infection..

Methods: The research design was a randomized pre-post-controlled design consisting of 2 treatment groups. The study was conducted in November 2022 until the sample size was met. The study samples were patients who had olfactory disorder and met the inclusion criteria who also willing to undergo INS and OT therapy. The treatment group was divided into 2 groups, namely the control group (OT) and treatment group (OT + INS). Treatment assessment was performed with Sniffin sticks test. Statistical tests were performed using IBM SPSS v25. Statistical test results were significant if the p value was <0.05.

Results: A total of 31 samples (16 OT samples and 15 OT+INS samples) were obtained for this study. The mean age in the OT group was 36.06±17.57 and 37.47±10.39 for the OT+INS group (p = 0.790). There was no significant difference in gender (p = 0.809) between groups 1 and 2. There was no significant difference between the treatment group and the control group on day 1, week 3, and week 6 for both right and left noses (p>0.05). There were significant differences in sniffin stick test scores on day 1 and week 3 and on day 1 and week 6 in both group 1 and group 2 (p < 0.001). There was no significant difference in the change of sniffin stick test score between OT group and OT + INS group at week 3 and week 6 (p>0.05).

Conclusions: OT therapy and the combination of OT + INS are effective to improve olfactory function by increasing sniffin stick scores at week 3 and week 6. There was an improvement in olfactory function for patients with olfactory disorders in this study. However, in patients with OT and INS combination therapy had better sniffin stick score.

1. Introduction

The function of smell in humans has an important role. Smell disorders can cause a person to lose the ability to detect smells. This condition of losing the ability to recognize smells is very dangerous for sufferers, where sufferers are unable to recognize dangerous substances in their environment. Apart from that, this condition also affects one's appetite, mental health and quality of life (Eibenstein et al., 2005).

Normal olfactory ability is defined as normosmia. Smell disorders can be in the form of anosmia (loss of the ability to smell), agnosia (not being able to smell one type of smell), partial anosmia, namely the inability to smell certain smells, hyposmia (decreased ability to

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smell in the form of sensitivity or quality of smell), dysosmia, namely wrong perception of smells, including parosmia and phantosmia, parosmia (change in the quality of olfactory sensation) while phantosmia (smell sensation without the presence of an odor stimulus/odorant hallucinations), presbyosmia (smell disturbance due to old age) (Wrobel and Leopold, 2005). In an OT management study, olfactory training was conducted for 12 weeks. Patients exposed themselves to four odors twice daily (phenyl ethyl alcohol (PEA): rose, eucalyptus, citronellal: lemon, and eugenol: clove). These four odors were chosen to represent the four odor categories claimed by Henning in his study called the "odor prism" (Geruchsprisma), in which he tried to identify primary odors. Olfactory testing was carried out before and after the 12-week training period using the Sniffin' Sticks test device, which includes testing for odor threshold, odor discrimination, and odor identification. This study provided the best results as follows: 1) olfaction training appeared to improve olfaction function in approximately 30% of subjects over a 12 week period alone compared to subjects who had no olfaction training; and 2) improvements were not only found in patients with loss of smell due to upper respiratory tract infections (URTI) and idiopathic loss of smell, but also in patients with functional anosmia after head trauma (Hummel et al., 2009).

2. Literature review

Smell System

The human olfactory system, which involves three key components in odor recognition. First, the olfactory neuroepithelium functions as a layer of cells in the nose that detects chemicals from the air. Next, these signals are sent to the olfactory bulb, a structure in the forebrain, which is responsible for processing and classifying olfactory information. Finally, the olfactory cortex, a higher part of the brain, receives these signals for interpretation, so that we can notice and recognize certain odors.

Smell Disorders

The causes of smell disorders can be grouped into three types: conductive disorders, sensory disorders, and neural disorders. Conductive disorders occur due to impaired transport or reduced odorant reaching the olfactory neuroepithelium, as well as disruption of the odorant's binding to the G protein (golf). In the case of conductive disorders, the pathology prevents the odorant from reaching the olfactory slits in the nasal cavity. Meanwhile, in sensorineural disorders, the dysfunction is related to the olfactory receptor neurons or their central projections (Goncalves and Goldstein, 2016).

Smell Function Examination involves several steps:

a. **History:** Questions about history of trauma, illness, and other factors that may affect smell.

b. **ENT-BKL Physical Examination:** Involves rhinoscopy to assess nasal obstruction such as polyps or inflammation.

c. **Imaging Examination:** Computed tomography and MRI are used to detect abnormalities in the brain or nose.

d. **Smell Chemosensory Examination:** Using special tests such as UPSIT, CCCRC, and “Sniffin Sticks” to stimulate the sense of smell with odorants and assess the response (Doty and Mishra, 2001; Hummel and Welge-Lüessen, 2006; Hummel and Lötsch, 2010)

3. Methods

Research design

This research is an experimental *clinical trial research* conducted on humans with a research design in the form of a randomized pre-postcontrolled design consisting of 2 groups. The control group (OT) and the treatment group (OT + INS) where variables were measured before and after treatment

Place and time

This research was carried out at the Hasanddin University Teaching Hospital (RS. UNHAS) and the Central General Hospital of Dr. Wahidin Sudirohusodo (RSWS). The research will be carried out in November 2022 until the sample size is met.

Research Sample

The research sample was taken using an *unmatched case control study technique* with an alpha value of 95% and a ratio of 8.92 so that 16 samples were obtained with OT therapy and 15 samples with OT and INS (Fleiss with CC). The estimated sample size in this study was measured using the *consecutive sampling method* using the formula below.

$$n = 2\left\{\frac{(Z\alpha + Z\beta)^2 S}{X_1 - X_2}\right\}^2$$

Information :

S : Estimated standard deviation of the variable

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m1-m2 : estimated mean difference
Z α : Alpha standard deviation value (1.96)
Z β : beta standard deviation value
n : sample size for one group

Inclusion and Exclusion Criteria

1. Inclusion Criteria
a. Age > 15 years and above.
b. It is not limited by race, ethnicity or gender
c. Patients with inflammation who experience impaired smell
d. Patients with post head trauma who experience smell disorders
2. Exclusion Criteria
a. Patients with decreased consciousness, shortness of breath and uncooperative therapy for OT and intranasal corticosteroids
b. Patients with ENT-BKL tumors
c. The patient has a congenital disease
d. Patients with degenerative diseases
e. Patients with a history of consuming systemic and inhaled drugs
f. The patient has a previous history of smell disorders
g. The patient had a history of previous rhinoplasty
h. Patients with a history of being immunocompromised

Research Subject Consent

In carrying out this research, every action was carried out with the permission and knowledge of the patient who was used as a research participant through an *informed consent sheet* and was declared to have met the ethical requirements for implementation from the Research Ethics Commission of Hasanuddin University Teaching Hospital (UNHAS Hospital) or Dr. Wahidin Sudirohusodo (RSWS).

Data analysis

The data obtained and the results are displayed in the form of narratives and tables or graphs. Data analysis used the SPSS version 25 program. The statistical analysis carried out was descriptive statistical calculations and frequency distribution, statistical tests using the Kolmogorov-Smirnov test to see the sample distribution, for the age distribution in the two samples carried out using the Independent t-test, Chi Square statistical test The test was carried out on both groups to see the difference between genders. To see the results of the comparison of smell function in the two groups, the Fisher Exact test, Chi Square test, and Independent t-test were carried out. Statistical test results are significant if the p value <0.05.

4. Results

Research has been carried out to assess the role of administering olfactory training and intranasal corticosteroids in improving olfactory function in patients with olfactory disorders in Makassar with sample characteristics based on age, gender and the cause of olfactory disorders.

Based on table 1, it can be seen that there is no significant difference in age (p = 0.790) between the control group (given *olfactory training*) and the treatment group (given *olfactory training + intranasal corticosteroids*) so that the data can be said to be homogeneous .

Based on table 2, it can be seen that there is no significant difference in gender (p = 1,000) between the control group (giving *olfactory training*) and the treatment group (giving *olfactory training + intranasal corticosteroids*).

no significant difference in the diagnosis of the cause of smell disorders (p = 0.630) between the control group (given *olfactory training*) and the treatment group (given *olfactory training + intranasal corticosteroids*) so that the data can be said to be homogeneous .

Based on table 4, it can be seen that the average sniffin stick test score on day 1 in the control group was (d: 5.13 ± 5.25; s: 4.75 ± 4.78) and in the treatment group (d: 6.67 ± 5.05; s: 6.47 ± 5.47). Average sniffin stick test score at week 3 in the control group (d: 14.38 ± 7.08; s: 14.75 ± 6.42) and in the treatment group (d: 17.40 ± 5.11; s: 18.73 ± 5.02). Average sniffin stick test score at week 6 in the control group (d: 23.94 ± 10.04; s: 24.38 ± 9.79) and in the treatment group (d: 27.72 ± 5.80 ; s: 28.13 ± 5.74). The average change in sniffin stick test scores from day 1 to week 3 in the control group (d: 9.25 ± 4.74; s: 10.00 ± 5.35) and in the treatment group (d: 10.73 ± 3.59; s: 12.27 ± 2.93). Meanwhile, the average change in sniffin stick test scores from day 1 to week 6 in the control group (d: 22.50 ± 4.38; s: 19.63 ± 8.60) and in the treatment group (d: 20.60 ± 6.15 ; s: 21.67 ± 5.31).

From the summary of the analysis results in table 5 based on the results of statistical tests, it was found that there was a difference in changes in the sniffin stick test scores between day 1 and week 3 and between day 1 and week 6 in both the control group and the treatment group. So it

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can be concluded that there is an influence of control (giving *olfactory training*) and treatment (giving *olfactory training + intranasal corticosteroids*) on changes in sniffin stick test scores in the 3rd week and 6th week.

From the summary of the analysis results in table 6 based on the results of statistical tests , it was found that there was no difference in changes in the sniffin stick test scores between the control group (giving *olfactory training*) and the treatment group (giving *olfactory training + intranasal corticosteroids*) at week 3 and week 3. 6 ($p > 0.05$).

5. Discussion

Sensory olfactory disorders are caused by the release of inflammatory mediators by lymphocytes, macrophages and eosinophils, which are toxic to olfactory neuroepithelial receptors, causing damage to the olfactory neuroepithelium (Cho, Seok Hyun , 2014). Anosmia and hyposmia are symptoms of Covid-19 infection. COVID-19-related olfactory dysfunction may occur due to several patholophysiologies, including obstruction of airflow to the receptors due to local inflammation and mucus changes in *the olfactory cleft* , downregulation of olfactory receptor proteins, damage to the olfactory neuroepithelium, and changes in central brain structures related to smell, especially in the *olfactory bulb* (Doty RL. 2016) .

Olfactory dysfunction can result from injury to any part of the olfactory tract, and most commonly occurs due to nasal trauma. In most situations, posttraumatic olfactory dysfunction results from distortion of the sinus tract. It can also result from direct injury to the olfactory nerve or injury to the central components or olfactory connections. (Kim Sw et al, 2017) .

OT has the potential to improve olfactory function also in healthy normosmic individuals, especially in those working in systems that require better olfactory function than normal people (Pieniak et al., 2022) . In post-COVID-19 infection patients, symptoms of anosmia or hyposmia can also be improved by performing OT twice for 12 weeks. This can be seen from improvements in quantitative olfactory function assessment parameters, such as the UPSIT-40, 10-point *visual analog scale,* and Sniffin Stick Test scores (Bérubé et al., 2023; Yaylacı et al., 2023) .

Olfactory training provides several changes that occur both anatomical, cellular and molecular. In the peripheral nervous system, there is an increase in the volume of the olfactory bulb after *idiopathic olfactory loss patients* and healthy people undergo OT therapy. This process may be obtained from a cascade of changes that occur in the central nervous system which is transmitted to the olfactory bulb (Mahmut et al., 2020; Negoias et al., 2017) .

Physiologically, OT can increase signal intensity and interneuron connections in the olfaction system. This is observed especially in *post-traumatic olfactory loss patients* (Hosseini et al., 2020; Pellegrino et al., 2019) . According to animal studies, OT may be able to promote the production of genes that control synaptic plasticity and olfactory receptors, such as the neurotrophic factor Olfr1507, the anti-apoptotic gene Bcl-2, and the neural and glial stem cell regulatory gene Gfap. All of these genes are responsible for the regeneration function of olfactory epithelial cells (Pieniak et al., 2022) .

Combination of OT and INS effective in improving the function of smell in patients with anosmia or hyposmia. The use of INS has indeed been recommended for olfactory dysfunction caused by sinonasal inflammatory disorders (Fokkens et al., 2020; Hummel et al., 2017; Miwa et al., 2020; Pieniak et al., 2022) . OT in several studies has shown its ability to increase the regeneration power of the olfactory epithelium, increase interneuron connectivity of the olfaction pathway, and improve the central hearing area in the anterior cerebral cortex (Hosseinpoor et al., 2022; Pieniak et al., 2022; Rashid et al., 2021) .

Fleiner et al., (2012) reported that there was a significant difference in improvement when compared between combination therapy of OT and INS with OT after 8 months of therapy. Significant differences were not found in therapy over a shorter period of time, namely 4 months. A study by Saussez et al., (2021) also showed something similar by administering therapy within two months. The combination of INS and OT is not significantly different from OT therapy alone in improving symptoms of olfactory dysfunction in mildly symptomatic COVID-19 patients.

Another study by Le et al. showed that a combination of OT and oral steroids for 10 weeks was more effective than OT alone only in COVID-19 patients. However, considering the systemic side effects of using oral

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corticosteroids for more than 2 weeks, the use of oral corticosteroids in patients with persistent olfactory dysfunction after COVID-19 is not recommended (Hopkins et al., 2021).

Concomitant OT therapy with local or systemic steroids has been used for the treatment of post-traumatic olfactory dysfunction (Fleiner 2012, Nguyen 2018, Bratt 2020). The proportion of clinically significant results in patients with combination therapy can reach up to 33% to 50%, which is higher than in the OT group alone. Anti-inflammatory therapy with steroids improves nerve recovery after olfactory nerve transection by suppressing the inflammatory reaction and reducing glial *scar formation* (Howell, 2018).

6. Conclusion

Sniffin Stick Test:

- First day: The majority of samples experienced anosmia and hyposmia.
- Week 3: Improvement occurs (hyposmia).
- Week 6: Some samples reached normal values (normosmia) in the control group (OT) and treatment group (OT + INS).

Effectiveness of Olfactory Training:

- Olfactory training and olfactory training + Intranasal Corticosteroid (INS) are effective in improving smell function (sniffin stick score) in the 3rd and 6th weeks.

Group Comparison:

- Improvement in olfactory function occurred in the control group (OT) and the treatment group (OT + INS).
- The treatment group showed a more significant increase in sniffin stick scores.

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Attachment

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Attachment

Table 1

Characteristics	Group		p
	Control (Olfactory training) (n:16)	Treatment (Olfactory training + Intranasal Corticosteroid) (n:15)	
	Mean ± SD Median	Mean ± SD Median	
Age (years)	36.06 ± 17.57 35.50	37.47 ± 10.39 31.0	0.790 _

Table 2

Characteristics	Group						p
	Control (olfactory training) (n:16)		Treatment (olfactory training + Intranasal Corticosteroid) (n:15)		Total		
	n	%	N	%	n	%	
Gender							
Man	5	33.3	5	31.3	10	35.5	1,000
Woman	10	66.7	11	68.8	21	62.5	

Table 3

Characteristics	Group						p
	Control (olfactory training) (n:16)		Treatment (olfactory training + Intranasal Corticosteroid) (n:15)		Total		
	n	%	N	%	n	%	
Diagnosis							
Post Covid 19	6	40.0	5	31.3	11	35.5	0.630
Post Nasal Os Fracture	1	6.7	0	0.0	1	3.2	
Post Mid Facial Fracture	1	6.7	0	0.0	1	3.2	
Post Nasal Trauma	0	0.0	1	6.3	1	3.2	
Persistent Allergic Rhinitis	1	6.7	1	6.3	2	6.5	
Chronic Rhinosinusitis	6	40.0	8	50.0	14	45.2	
History of Os Nasal Trauma	0	0.0	1	6.3	1	3.2	

Table 4

Measurement Time	Smell Disorders	Group				p
		Treatment (olfactory training+Intranasal Corticosteroid)		Control (olfactory training) (n:16)		
		n	%	n	%	
Day 1	Dextra Anosmia	14	93.3	16	100.0	0. 294*
	Hyposmia	1	6.7	0	0.0	
	Normosmia	0	0.0	0	0.0	

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	Sinistra					
	Anosmia	14	93.3	16	100.0	0. 294*
	Hyposmia	1	6.7	0	0.0	
	Normosmia	0	0.0	0	0.0	
Week 3	Dextra					
	Anosmia	4	26.7	7	43.8	0.320*
	Hyposmia	11	73.3	9	56.3	
	Normosmia	0	0.0	0	0.0	
	Sinistra					
	Anosmia	4	26.7	7	43.8	0.320*
	Hyposmia	11	73.3	9	56.3	
	Normosmia	0	0.0	0	0.0	
Week 6	Dextra					
	Anosmia	1	6.7	2	12.5	0.646**
	Hyposmia	8	53.3	6	37.5	
	Normosmia	6	40.0	8	50.0	
	Sinistra					
	Anosmia	1	6.7	2	12.5	0.646**
	Hyposmia	8	53.3	6	37.5	
	Normosmia	6	40.0	8	50.0	

Table 5

Group	Location	Measurement Time	Sniffin Stick Score		p
			Mean±SD	Difference	
Control	Dextra	Day 1	5.13±5.25	9.25 ± 4.74	<0.001
		Week 3	14.38 ± 7.08		
		Day 1	4.75 ± 4.78	10.00 ± 5.35	<0.001
		Week 6	14.75 ± 6.42		
	Sinistra	Day 1	5.13±5.25	18.81 ± 8.45	<0.001
		Week 3	23.94 ± 10.04		
		Day 1	4.75 ± 4.78	19.63 ± 8.60	<0.001
		Week 6	24.38 ± 9.79		
Treatment	Dextra	Day 1	6.67±5.05	10.73 ± 3.59	<0.001
		Week 3	17.40 ± 5.11		
		Day 1	6.47 ± 5.47	20.60 ± 6.15	<0.001
		Week 6	27.27 ± 5.80		
	Sinistra	Day 1	6.67±5.05	12.27 ± 2.93	<0.001
		Week 3	28.21 ± 4.66		
		Day 1	6.47 ± 5.47	21.67 ± 5.31	<0.001
		Week 6	28.13 ± 5.74		

Table 6

Measurement Time	Location	Group	Sniffin Stick Score		p
			Mean±SD	Difference	
Week Changes 3-1	Dextra	Control	9.25 ± 4.74	1.48 ± 1.51	0.337
		Treatment	10.73 ± 3.59		

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	Sinistra	Control Treatment	10.00 ± 5.35 12.27 ± 2.93	2.26 ± 1.53	0.262
Week Changes 6-1	Dextra	Control Treatment	18.81 ± 8.45 20.60 ± 6.15	1.78 ± 2.67	0.509
	Sinistra	Control Treatment	19.63 ± 8.60 21.67 ± 5.31	2.59 ± 3.55	0.437