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Assessment of Olfactory Functions in Patients with Acne vulgaris Under Systemic Treatment: A Prospective Study

Sistemik Tedavi Alan Akne Vulgaris Hastalarında Koku Fonksiyonlarının Değerlendirilmesi: Prospektif Bir Çalışma

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ABSTRACT

AIM: The loss of smell is a common disease and can affect a patient's quality of life. Olfactory disturbance leads to problems such as safety and eating. Acne vulgaris is a prevalent disease in the daily clinical practice of a dermatologist. Doxycycline and isotretinoin are the most preferred systemic drugs for severe acne. This study aimed to investigate the possible effects on olfactory function in patients with acne vulgaris receiving isotretinoin and doxycycline therapy by using the Brief Smell Identification Test.

MATERIAL AND METHOD: A total of 60 patients with acne vulgaris were included in the study. The patients were divided into two groups, each consisting of 30 patients. One group received oral doxycycline, while the other received oral isotretinoin. The olfactory function of each patient in both groups was assessed at the beginning and third month of treatment by using the Brief Smell Identification Test.

RESULTS: There was no statistically significant difference between the total scores of the Brief Smell Identification Test at 0. and 3. months in both the isotretinoin group and the doxycycline group.

CONCLUSION: The results of the present study showed that both drugs are safe and have no undesirable effect on olfactory function. However, the certain effects of both drugs on olfactory functions still remain unknown. New studies are needed to shed light on this issue.

Keywords: Acne, isotretinoin, doxycycline, olfactory function, smell

ÖZET

AMAÇ: Koku kaybı sık görülen bir hastalıktır ve hastanın yaşam kalitesini etkileyebilir. Koku alma bozukluğu hastaların günlük hayatında güvenlik ve yeme gibi sorunlara yol açar. Akne vulgaris, bir dermatoloğun günlük klinik pratiğinde sık görülen bir hastalıktır. Doksisiklin ve isotretinoin, şiddetli akne için en çok tercih edilen sistemik ilaçlardır. Bu çalışmada, 'Brief Smell İdentification Test' kullanılarak isotretinoin ve doksisiklin tedavisi alan akne vulgarisli hastalarda koku alma fonksiyonu üzerindeki olası etkiler araştırılmıştır.

GEREÇ VE YÖNTEM: Çalışmaya toplam 60 akne vulgaris hastası dahil edildi. Hastalar her biri 30 hastadan oluşan iki gruba ayrıldı. Bir grup oral doksisiklin alırken, diğer grup oral isotretinoin aldı. Her iki gruptaki her hastanın koku alma fonksiyonu, tedavi başlangıcında ve üçüncü ayda 'Brief Smell Identification Test' kullanılarak değerlendirildi.

BULGULAR: Hem isotretinoin grubunda hem de doksisiklin grubunda 0. ve 3. aylardaki 'Brief Smell Identification Test'toplam skorları arasında istatistiksel olarak anlamlı bir fark yoktu.

SONUÇ: Mevcut çalışmanın sonuçları her iki ilacın da güvenli olduğunu ve koku alma fonksiyonu üzerinde istenmeyen bir etkisinin olmadığını göstermiştir. Ancak her iki ilacın da koku alma fonksiyonları üzerindeki kesin etkileri hala bilinmemektedir. Bu konunun aydınlatılabilmesi için yeni çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Akne, izotretinoin, doksisiklin, koku fonksiyonu, koku

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INTRODUCTION

The loss of smell is a common disease which can significantly affect patients' quality of life. The disease has been underlined and accepted as a public health concern during the coronavirus disease 2019 (COVID-19) pandemic.[1]

There are many different causes of olfactory dysfunction, such as head traumas, upper respiratory tract infections and exposure to toxins. [2] Olfactory disturbance may lead to many problems in daily life, especially in the areas of safety and eating. An anosmic or hiposmic patient may not be able to detect the warning odours of spoiled food, smoke, or leaking gas. In addition to all these disadvantages, a loss of sense of smell can lead to a lack of food taste.[3,4]

Acne vulgaris is one of the most common dermatological diseases in daily clinical practice. It usually affects adolescents and young adults and sometimes may have the potential to cause scarring. Systemic treatment is necessary in patients with severe acne to prevent psychological and social impairment. There are several choices of systemic therapy for acne, including oral antibiotics (mainly doxycycline), isotretinoin and hormonal treatment. [5]

Oral antibiotics may be the treatment choice for acne in individuals resistant to topical treatments. Among other alternatives, oral tetracyclines are the most preferred ones all around the world. [6] Doxycycline is the only form which is on sale in our country. Thus, it is the most commonly prescribed oral antibiotic form. Isotretinoin is a synthetic analogue of vitamin A, which is indicated for recalcitrant acne. Both systemic medications may have some side effects, but most of them are mild and tolerable.

There are many studies in the literature investigating the side effects of systemic acne treatment. Only a few reported the possible effects of isotretinoin and doxycycline on olfactory functions. Some of these studies reported positive effects on olfactory function, on the other hand, some of them reported negative effects. [7-13] The certain effects on olfactory functions in the patients receiving systemic acne treatment remain unknown. This study aimed to investigate the possible impact on olfactory function in patients with acne vulgaris receiving isotretinoin and doxycycline therapy using the Brief Smell Identification Test.

MATERIAL AND METHOD

A total of 60 patients with acne vulgaris who were admitted to the Department of Dermatology of xxx Hospital between October 2022 and October 2023 and who received either isotretinoin or doxycycline were included in the study. The local ethics committee approved the study (E-22-896). All participants were informed about the study, and a written consent form was obtained. The study was performed by the latest version of the 'Helsinki Declaration' and 'Guidelines for Good Clinical Practice'.

The study consisted of two groups, each of which included 30 patients. One group received oral doxycycline, while the other received oral isotretinoin. All of the patients underwent a careful rhinological examination at the ENT and Head and Neck Surgery Clinic of xxx Hospital before including in the study. Patients with septal deviation, allergic rhinitis, nasal polyposis or rhinosinusitis, diabetes mellitus or neurological defects were not included. The ones who were smokers or were receiving drugs that could affect olfaction, such as calcium channel blockers, ACE inhibitors, diuretics, statins or antidepressants, were also not included. Additionally, the patients using vitamin A supplements or who had a recent history of any psychiatric disorder were also excluded. Those who were pregnant or under 18 years of age were not included in either group.

The demographic characteristics of each patient group, such as age and sex, were recorded. A daily dose of 0,5-1 mg/kg isotretinoin was initiated in the isotretinoin group. Doxycycline was initiated as 100 mg/day together with topical benzoyl peroxide in the doxycycline group. The total cumulative dose of isotretinoin was also calculated and recorded.

The olfactory function of each patient in both groups was assessed at the beginning and third month of treatment by using the Brief Smell Identification Test. The Brief Smell Identification Test (BSIT) is a brief, easily administered, and convenient instrument that was developed as a quick tool to measure odor identification deficits. It is a shortened version of Pennsylvania Smell Identification Test (UPSIT) with 40-items. [14] The Turkish version of the modified BSIT (Sensonics Inc.; Haddon Heights, NJ, USA) was used in this study. In previous studies, it was reported that the UPSIT included some smells which were not distinguished by the Turkish population, and therefore, they modified the UPSIT to contain odours recognized by the Turkish population. That's the reason why we used the Turkish version of BSIT. The BSIT comprises 12 items selected from the 40-item UPSIT (Sensonics Inc.; Haddon Heights, NJ, USA). The two tests are highly correlated. The BSIT is a 'scratch and sniff' test, including four options for each question. All of the patients were asked to release the smell and select the option that identified the odour. The patients were requested to answer all of the 12 questions, and if they were not sure, they were asked to choose the closest one. A mini period of 30 seconds was given to the patients between each odour. The test was administered by the same doctor in a well-ventilated room. The applying doctor did not use perfume or powdered gloves. The BSIT included 12 odors: mint, banana, clove, gas oil, strawberry, pine, cinnamon, smut, lemon, soap, baby powder and rose. In the end, a total score was calculated. The score reflected the number of correct answers. [15] The patients with a total score of 9-12 were classified as normal olfactory nerve function; while those with a score of fewer than 9 were classified as decreased olfactory nerve function. The test was applied at the beginning and third month of the treatment in both groups.

Statistical Analysis

All data were analysed using the IBM Statistical Package for the Social Sciences (SPSS) version 21.0. The normality distribution of scale variables was checked using the Kolmogorov-Smirnov test. Data were expressed as median (interquartile range) or mean ± standard deviation for those with nonparametric or parametric distribution, respectively. Independent samples were compared with the Student's T test or Mann-Whitney U test, whichever is appropriate. Dependent samples were compared with the Wilcoxon signed rank test. Correlation analysis in nonparametric data was done with Spearman's rho test. Pearson's chi-square test was used for categorical variables, and Fisher's Exact test was used if at least one cell had an expected count of less than 5. Dependent categorical variables were compared with McNemar's test. Two-sided p-values less than 0.05 were considered statistically significant.

RESULTS

In this prospective comparative study consisting of 60 patients with acne vulgaris, there were 30 patients in the isotretinoin group and 30 patients in the doxycycline group. Isotretinoin group and doxycycline study group had similar sex, age, severity and duration of acne vulgaris (p=0.573, p=0.176, p=1, p=0,747, respectively)

Table 1: Demographic and clinical characteristics of isotretinoin and doxycycline groups

	Isotretinoin group (n=30)		Doxycycline group (n=30)	P
Sex (n /%)				
Female	22 (73.3%)		20 (66.7%)	
Male	8 (26.7%)		10 (33.3%)	0.573
Age (Mean±SD, years)	21.03±4.86		22.97±6.01	0.176
Severity of acne vulgaris (n /%)				
Moderate	20 (66.7%)		21 (70%)	
Severe	9 (30%)		9 (30%)	1*
Very Severe	1 (3.3%)		0 (0%)	
Duration of acne vulgaris (median/minimum, maximum, IQR, months)	21 (min:5, max:120, IQR:31.5)		24 (min:3, max:96, IQR:36)	0.747

SD: standard deviation, IQR: interquartile range

Data were expressed as mean±SD, median, minimum, maximum and IQR in continuous variables and n (%) in categoric variables.

Categorical data were compared using the Chi-Square test. Fisher's exact test was used to compare the severity of acne between groups. Severe and very severe subgroups were combined since they had expected counts less than 5.

Independent samples were compared with the Student's T and Mann–Whitney U tests.

Median total cumulative drug dose in the isotretinoin group was 2400 mg (min:600, max:3600, IQR:1200).

The mean BSIT score before treatment in the isotretinoin group was 9 (min:6, max:11, IQR:2) and 8.5 (min:5, max:12, IQR:3) in the doxycycline group. The mean scores in the third month of treatment were 9 (min:3, max:11, IQR:2) in the isotretinoin group and 9 (min:5, max:12, IQR:3) in the doxycycline group, respectively. There was no statistically significant difference in the total score of the brief smell identification test applied at the beginning of treatment (month 0) and in the 3rd month of treatment (month 3) between the isotretinoin group and doxycycline study group (p=0.247, p=0.845, respectively) (Table 2). There was no statistically significant difference between the total scores of the brief smell identification test at 0. and 3. months in both the isotretinoin group and the doxycycline group (p=0.240, p=0.578, respectively)

Table 2: Comparison of the total score of brief smell identification test at the beginning of treatment (month 0) and in the 3rd month of treatment in isotretinoin and doxycycline groups

	Isotretinoin group (n=30)	Doxycycline group (n=30)	P
Total score, month 0 (median/minimum, maximum, IQR)	9 (min:6, max:11, IQR:2)	8.5 (min:5, max:12, IQR:3)	p=0.247*
Total score, month 3 (median/minimum, maximum, IQR)	9 (min:3, max:11, IQR:2)	9 (min:5, max:12, IQR:3)	p=0.845*
	p=0.240**	p=0.845**	

Continuous variables expressed data as median (minimum, maximum, interquartile range).
Independent samples were compared with the Mann-Whitney U test; dependent samples were compared with the Wilcoxon Signed Rank test.
* Mann Whitney U test
** Wilcoxon Signed Rank test
IQR: Interquartile range

No statistically significant difference was found between males and females in terms of having decreased and normal olfactory nerve function according to BSIT at baseline and in the 3rd month of treatment in either the isotretinoin group, or in the doxycycline group (isotretinoin group month 0, month 3: p=0.643, p=0.417; doxycycline group month 0, month 3: p=0.245, p=0.602, respectively).

No statistically significant difference was found in the number of patients with decreased and normal olfactory nerve function according to BSIT applied at the beginning of treatment (month 0) and in the 3rd month of treatment between the isotretinoin group and doxycycline study group (p=0.063, p=0.598, respectively)

Table 3: Comparison of olfactory nerve function according to brief smell identification test at the beginning of treatment (month 0) and in the 3rd month of treatment in isotretinoin and doxycycline groups

	Isotretinoin group (n=30)		Doxycycline group (n=30)		P
	Month 0	Month 3	Month 0	Month 3	
Decreased olfactory nerve function n/%	8 (26.7%)	11 (36.7%)	15 (50%)	13 (43.3%)	Month 0: p=0.063*
Normal olfactory nerve function n/%	22 (73.3%)	19 (63.3%)	15 (50%)	17 (56.7%)	Month 3: p=0.598*
	Month 0 vs Month 3: p=0.549**		Month 0 vs Month 3: p=0.774**		

Data were expressed as n/% in categorical variables.
Categorical independent data were compared using the Chi-Square test. McNemar's test compared categorical independent data. If at least 1 cell had expected count of less than 5, binominal distribution was used.
*Chi-Square ** McNemar's test

There was also no statistically significant difference between the number of patients with decreased and normal olfactory nerve function according to BSIT applied at 0. and 3. months in both the isotretinoin group and the doxycycline group (p=0.549 p=0.774, respectively) (Table 3). There was no statistically significant correlation between the total cumulative dose of isotretinoin and the total score of BSIT in the isotretinoin group (r=-0.098, p=0.606)

DISCUSSION

Acne vulgaris, which is one of the most common diseases in dermatology, is associated with physical and psychological morbidity and results in a considerable expense annually for each country. Systemic antibiotics may be prescribed for moderate to severe acne or inflammatory acne, that is resistant to topical therapies. Oral isotretinoin is the best choice for a physician when the patient has severe nodular acne or moderate acne, when it causes scarring and when the patient is distressed. Serious side effects are uncommon with either systemic therapy. [16]

The fact that isotretinoin causes many multisystem side effects is already known. Mucocutaneous side effects, such as xerosis, skin fragility, erythemal changes, pruritus or rashes, are the most common and less severe adverse events. But the drug may also cause other side effects, including other systems (ophthalmic, nasopharyngeal, oral, mood and neurological, musculoskeletal, gastrointestinal, liver function test abnormalities, lipid panel abnormalities, blood count abnormalities, urine and kidney function test abnormalities). [17] Nasopharyngeal changes include dry nose, epistaxis, and dryness of other mucosal tissues. These changes are usually dose-related and moisturising the mucous membranes usually decreases their severity. [18]In the literature, only a few case reports and studies report its adverse effects on the sense of smell. [7,8, 19-23]

Heise et al. reported an interesting case with an olfactory and taste disturbance after acne treatment with isotretinoin. The patient was a 36-year-old man with severe acne and was advised to use isotretinoin at a daily dose of 0,5-0,75 mg/kg for 4 months. He reported an olfactory disturbance after 4 months and experienced a change in taste after 6 months. He also had 12 kg weight loss within 2 months. The patient did not have any history of viral infection, head trauma or other medications. Endoscopic examination of the nose and a CT scan showed no evidence of polyposis, chronic sinusitis or neoplasm. His status had been reported as not changed after stopping the treatment and beginning systemic steroids after 11 months . [8] Kartal et al. reported a study in which 45 patients with acne treated with isotretinoin underwent olfactory function tests (Sniffin' Sticks Test) at baseline and third month of treatment. They found a statistically significant difference in olfactory functions of the patients in favour of improving olfactory functions. The authors concluded that isotretinoin therapy improved the sense of smell. [7] Kuş et al. [19] investigated 102 acne patients using oral isotretinoin or topical treatments during the COVID-19 pandemic. They concluded that the use of oral isotretinoin did not cause an increase or decrease in the risk of COVID-19 transmission when compared with the topical treatment group. Still, the patients using oral isotretinoin had a lower incidence of taste/smell loss and headache. The authors cited studies that were carried out on mice and reported that retinoic acid treatment in mice increased the number of macrophages expressing retinoic acid receptors, leading to a faster recovery of olfactory function. [10,20] They suggested that the lower incidence of taste/smell loss in the oral isotretinoin group could be related to the faster recovery of olfactory function with isotretinoin. [19] Haglin et al. analysed male and fema-

le mice to investigate the cellular and molecular basis of metaplasia and declining neurogenesis in the ageing olfactory epithelium. Their study demonstrated that CYP26B1, a neural activity-regulated gene, is an essential spatial stem cell regulator in a neuroepithelium where changes in retinoic acid influence age-related tissue pathology. They suggested that retinoic acid serves to delay olfactory stem cell ageing. [21] Chung TW et al. reported a pilot study investigating the effect of short-course oral vitamin A (25000 IU/day for 14 days) and aerosolised diffuser olfactory training in the treatment of persistent olfactory dysfunction in long COVID. They concluded that a combination of these therapies would be effective on the symptoms of the patients suffering from olfactory dysfunction in long COVID. They suggested that their findings sustain the potential for vitamin A as a supportive therapy in promoting neuronal recovery. It was revealed that vitamin A could be applied to various olfactory neurosensory disorders, and also it could be a good topic in investigating regenerative medicine beyond the olfactory system. [22]

In this study, the mean scores of BSIT before and at the 3rd month of isotretinoin treatment were not statistically significantly different. Although the sense of smell of a few patients was examined to increase or decrease within 3 months, there seemed to be no significant effect on the sense of smell in total. This result may be due to the small number of patients. To determine the exact role of retinoids on olfactory dysfunction, prospective, controlled and long-term studies with a larger number of patients are needed.

Doxycycline was first approved by the FDA in 1967, and it is the first tetracycline derivative to come to market. It is more lipophilic when compared to tetracycline, making it more optimal for penetrating and accumulating in the sebaceous gland. The drug's side effects are more tolerable than tetracycline, but still, there are potential adverse effects that the clinician should be aware of. Phototoxicity, gastrointestinal disturbance, and tooth discoloration in individuals with developing teeth, are some common and well-known side effects. Fortunately, it is possible to avoid these side effects by paying attention to certain rules and taking precautions. Its success in treating acne is not only related to antimicrobial activity but also its anti-inflammatory activity as well. [23] There are no case reports or studies in the present literature investigating the potential effects of doxycycline on olfactory functions in acne patients. However, there are some studies revealing the potential positive effects on olfactory functions in those patients treated with doxycycline in indications other than acne . [11-13]

Çetin et al. reported that an add-on therapy with doxycycline in patients diagnosed with chronic rhinosinusitis with nasal polyp (CRSwNP), which has a high symptom burden, could be considered and found to be effective, especially CRSwNP comorbid with asthma. [11] In another study, Nabavi et al. also revealed that CRSwNP is a complex disorder, and effective treatment remains a major challenge. Antibiotics with anti-inflammatory properties, such as doxycycline, could have the potential to be an adjunct therapy in the management of chronic airway inflammation. They found that doxycycline improves the quality of life of patients with CRSwNP and also has beneficial effects on improving the sense of smell. [12] Jenkins et al. investigated the effects of oral administration of metronidazole and doxycycline on the olfactory capability of explosives detection dogs. While metronidazole administration resulted in the degradation of the detection threshold for 2-3 explosives, no significant effect was found in the degradation of detection thresholds with doxycycline administration. Finally, doxycycline was offered as a safe drug for use in explosives detection dogs . [13]

This study found no significant effect on olfactory functions in patients with acne vulgaris receiving doxycycline therapy. This result could be again due to the small number of patients. Since this is the first study investigating the drug's possible effects on acne patients, more studies are needed to come to an exact conclusion about the real impact on olfactory functions of acne patients.

As revealed before, the study has some limitations. Firstly, a larger number of patients are needed. Also, a longer follow-up duration, including a period after stopping the treatments, could be added. Another limitation is that the study does not include a healthy control group.

CONCLUSIONS

This study investigated the possible effects of systemic acne treatment with isotretinoin and doxycycline on olfactory functions. It can be concluded that both drugs are safe and have no undesirable effect on olfactory function. However, the exact effects of both drugs-either positive or negative-on olfactory functions still remain unknown. We hope this study will call attention to this interesting topic and find more satisfactory answers in future studies.

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