

Effects of Oral Isotretinoin Therapy on Nasal Dryness and Nasal Obstruction in Patients with Acne Vulgaris: Objective and Subjective Assessments Based on the Dose and Duration of Therapy

Enes Yiğit¹, Duygu Erdil², Zehra Çınar¹, Efe Can¹, Özgür Yiğit¹

¹University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Otorhinolaryngology, İstanbul, Turkey

²University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Dermatology, İstanbul, Turkey

ABSTRACT

Introduction: This study aimed to evaluate the effect of oral isotretinoin therapy on nasal dryness and nasal obstruction in patients with acne vulgaris.

Methods: A total of 102 patients with acne vulgaris (mean \pm standard deviation age, 21.1 \pm 3.4 years; female, 64.7%) initiating systemic isotretinoin treatment [in 0.25 mg/kg/day (n=35) or 0.5 mg/kg/day (n=67) doses] were enrolled in this prospective study. Data on nasal obstruction [via nasal obstruction symptom evaluation (NOSE)] and nasal dryness via a psychometric response scale [visual analog scale (VAS)] and nasal Schirmer test values (right and left Schirmer values) were recorded at baseline. Nasal dryness (VAS and nasal Schirmer test) and nasal obstruction (NOSE) assessments were repeated at months 2 and 4 of treatment in isotretinoin groups.

Results: The right Schirmer values at month 2 ($p<0.05$) in the 0.25 mg isotretinoin group and right ($p<0.01$ for each) and left ($p<0.001$ and $p<0.01$, respectively) Schirmer values at months 2 and 4 in the 0.5 mg isotretinoin group significantly decreased from baseline, while VAS scores at months 2 and 4 ($p<0.001$ and $p<0.01$, respectively) significantly increased in the 0.5 mg isotretinoin group.

Conclusion: Our findings revealed the association of isotretinoin treatment with the occurrence of nasal dryness but not with nasal obstruction in patients with acne vulgaris, particularly with the high-dose daily regimen, regardless of treatment duration. The nasal Schirmer test is an objective assessment of nasal dryness in patients receiving isotretinoin therapy and the potential benefit of low-dose isotretinoin in reducing the risk of nasal dryness.

Keywords: Nasal dryness, nasal obstruction, isotretinoin dose, acne vulgaris, nasal Schirmer test

Introduction

Isotretinoin, used orally, is successfully used for acne treatment for more than two decades. It is a first-generation retinoid with pleiotropic effects on etiological factors involved in acne pathogenesis such as keratinocyte differentiation, proliferation, and sebaceous gland activity (1-3). However, the mechanism of action is considered to adversely affect mucociliary regrowth, refunctioning, and clearance properties of the nasal epithelium (4,5).

Nasal secretion plays a vital role in humidification, heating, and cleaning of inspired air and participates in the first-line defense of the respiratory tract (6-9). Notably, the viscosity, elasticity, and adhesion properties of the mucus are important in mucociliary clearance and thus in the prevention of mucous stasis, secondary infection, and chronic dryness (4,5,8).

Several studies have reported that isotretinoin was associated with negative effects on the nasal mucosa and mucociliary functions, including the induced epithelial and mucociliary differentiation, inhibition of squamous cell differentiation, and impaired mucociliary clearance time (MCT) (4,5,10-13). However, despite the consideration of reduction in mucosal secretion and dryness of the nasal surface mucosa in the etiology of the two common side effects of isotretinoin treatment including the prolonged MCT and the epistaxis (2,4,5,12-15), nasal dryness has not been extensively studied using objective measures in patients receiving isotretinoin.

Problems related to nasal secretion (sensation of a dry or runny nose) are among the most frequent patient-reported complaints in otolaryngology practice (8,16). However, their diagnosis is mainly based on the subjective clinical description, as only a few objective tests are



Address for Correspondence: Enes Yiğit MD, University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Otorhinolaryngology, İstanbul, Turkey
Phone: +90 554 470 11 80 E-mail: enessyigit@hotmail.com ORCID ID: orcid.org/0000-0002-9853-6238

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available for measuring nasal humidity with limited use in routine clinical practice because of the need for special equipment or associated patient discomfort (7,9,16-18).

As the nasal Schirmer test is an easily applicable, low-cost, and rapid tool in the objective assessment of nasal secretion and nasal mucosal moisture, it is considered promising in this regard (7,9,16). Thus, the nasal Schirmer test, a modified version of the Schirmer test used in evaluating lacrimation in ophthalmology practice, is now increasingly used in otolaryngology practice in evaluating the amount of nasal secretion (7,9,16).

This study aimed to investigate the effect of oral isotretinoin therapy on nasal dryness and nasal obstruction through objective (Schirmer values) and subjective [visual analog scale (VAS), nasal obstruction symptom evaluation (NOSE) scores] measures, with respect to the dose and duration of therapy in patients with acne vulgaris.

Methods

Study Population

A total of 102 dermatology outpatients [mean \pm standard deviation (SD) age, 20.9 \pm 3.3 years; female, 65.1%] initiating systemic isotretinoin treatment [in 0.25 mg/kg/day (n=35) or 0.5 mg/kg/day (n=67) doses] for acne vulgaris were enrolled in this prospective 4-month isotretinoin follow-up study. The study was conducted at a tertiary care otolaryngology clinic. Patients with a history of nasal surgery, upper respiratory tract infection within the last 4 weeks, active or ex-smokers, and took topical or systemic medication (i.e., steroids), and had rhinitis, chronic sinusitis, nasal polyp, septum deviation, chronic otitis media, concha hypertrophy, or any systemic disease were excluded from the study.

Written informed consent was obtained from each patient. The study was conducted following the ethical principles stated in the Declaration of Helsinki and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2501, date: 21/08/2020).

Assessments

Data on patient demographics (age and gender), isotretinoin dose, nasal obstruction (via NOSE), and nasal dryness via a psychometric response scale (VAS; 0, none; 10, worst) and nasal Schirmer test values (right and left Schirmer values) were recorded at baseline. Nasal dryness (by VAS and nasal Schirmer test) and nasal obstruction (by NOSE) assessments were repeated at months 2 and 4 of treatment in isotretinoin groups (0.25 and 0.5 mg/kg/day).

NOSE Questionnaire

NOSE questionnaire, developed by Stewart et al. (19) in 2004, is a 5-item questionnaire with each item scored from 0 to 4. For total scores, each answer is multiplied by 5 to base the scale out of a possible score of 100 (most severe nasal obstruction) for analysis as previously described, whereby higher scores demonstrate more severe nasal obstruction (19,20). Adaptation and validation of the Turkish version of the NOSE questionnaire were performed by Onerci Celebi et al. (21) in 2018.

Nasal Schirmer Test

Before the procedure, patients were asked to irrigate their noses with tap water and to wait for 15 min in a room with 22.5 °C temperature and 33.8% humidity to adapt to the hospital environment. Whatman no. 41 strips of filter paper, known as the Schirmer test filter paper, with 35 mm length and 5 mm width (Dr. Gerhard Mann Chem. Pharm Fabrik GmbH Berlin, Germany) were used for all subjects. The moistened area on the strip removed from each nostril was recorded as left and right (bilateral) Schirmer values (in mm) as previously described (7,9).

Statistical Analysis

Statistical analysis was made by using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2013). The Mann-Whitney U test, Friedman test, and Wilcoxon test with Bonferroni correction were used for the analysis of non-normally distributed numerical variables. Data were expressed as mean \pm SD, median (minimum-maximum), and percent (%) where appropriate; $p < 0.05$ was considered significant.

Results

Baseline Characteristics

The mean \pm SD of the patient age was 21.1 \pm 3.4 (range: 16-34) years, and 64.7% of the patients were female. The daily dose of isotretinoin was 0.25 mg/kg in 35 (34.3%) patients and 0.5 mg/kg in 67 (65.7%) patients. Overall, 60 and 46 patients adhered to month 2 and 4 visits, respectively. The daily isotretinoin dose was 0.5 mg/kg in 39 (65.0%) of 60 patients assessed at month 2 visit and 32 (69.6%) of 46 patients assessed at month 4 visit.

Study Parameters in All Patients Treated with Isotretinoin

When compared with pretreatment values, months 2 and 4 of isotretinoin treatment were associated with a significant increase in VAS scores [median (minimum-maximum), 0 (0-7) vs 3 (0.7) and 3 (0-9), $p < 0.001$ each] and a significant decrease in both left [median (minimum-maximum), 19 (9-35) vs 17 (7-30) and 15 (5-35), $p < 0.001$ each] and right [median (minimum-maximum), 17 (10-35) vs 15 (9-35) and 15 (4-35), $p < 0.001$ each] Schirmer values. Month 4 left Schirmer values were also significantly lower than month 2 values ($p < 0.05$) (Table 1, Figure 1).

Study Parameters in Isotretinoin Groups

No significant difference was noted between isotretinoin groups in terms of pretreatment and posttreatment month 2 and 4 VAS and NOSE scores and the right and left Schirmer values (Table 2).

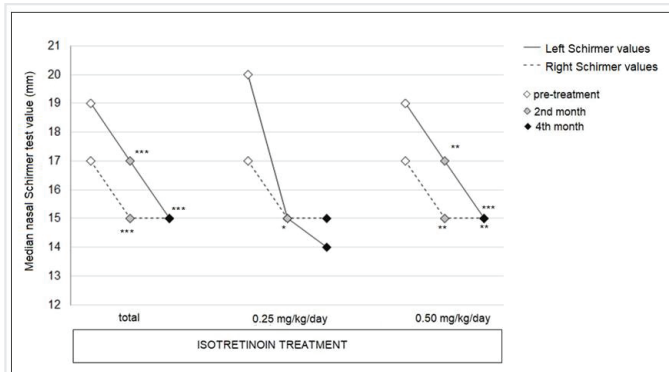
In the 0.25 mg isotretinoin group, the only significant change from baseline was observed for month 2 right Schirmer values ($p < 0.05$), with no significant change from baseline in month 2 VAS, NOSE, and left Schirmer values as well as in month 4 VAS, NOSE, and bilateral Schirmer values (Table 2, Figure 1).

In the 0.5 mg isotretinoin group, when compared with pretreatment values, month 2 and 4 therapy was associated with significantly increased VAS scores ($p < 0.001$ and $p < 0.01$, respectively) and

Table 1. Study parameters in all patients treated with isotretinoin

		Pretreatment (n=102)	Month 2 (n=60)	Month 4 (n=46)	p ¹
VAS score	Mean ± SD	1±2	3±2*	4±3*	<0.001
	Median (min.-max.)	0 (0-7)	3 (0-7)	3 (0-9)	
NOSE score	Median (min.-max.)	0 (0-40)	0 (0-40)	5 (0-35)	0.705
Nasal Schirmer test					
Right Schirmer value	Mean ± SD	20±6	17±6*	16±7*	<0.001
	Median (min.-max.)	17 (10-35)	15 (9-35)	15 (4-35)	
Left Schirmer value	Mean ± SD	20±6	17±6*	16±7*+*	<0.001
	Median (min.-max.)	19 (9-35)	17 (7-30)	15 (5-35)	

VAS: Visual analog scale, NOSE: nose obstruction symptom evaluation, SD: standard deviation, min.: minimum, max.: maximum, 1: Friedman test, *: p<0.001 compared with pretreatment values (Wilcoxon test with Bonferroni correction, p<0.016), +: p<0.05 compared with month 2 values (Wilcoxon test with Bonferroni correction, p<0.016)

**Figure 1.** Nasal Schirmer test findings: right and left Schirmer values in all groups and isotretinoin groups, at baseline and months 2 and 4 of treatment

*, p<0.05, **, p<0.01, and ***: p<0.001; compared with pretreatment values

significantly decreased right (p<0.01 for each) and left (p<0.001 and p<0.01, respectively) Schirmer values (Table 2, Figure 1).

Discussion

Our findings revealed a significant increase in nasal dryness measured via VAS scores and bilateral nasal Schirmer values in patients with isotretinoin-treated acne vulgaris, particularly when the daily dose was set at 0.5 mg/kg, even within 2 months of therapy. NOSE scores reported by patients at baseline and during treatment were associated with the lack of nasal obstruction; thus, isotretinoin treatment had no significant effect on NOSE scores, regardless of the treatment dose or duration.

In the present study, the significant increase in nasal dryness scores based on both subjective (increase in VAS scores) and objective (decrease in right and left Schirmer values) measures in patients who received isotretinoin supports the consideration of mucosal dryness as the most common side effect of isotretinoin, i.e., patients on isotretinoin twice likely complained of nasal dryness compared with healthy individuals (2,22).

The bilateral Schirmer values recorded at baseline in the present study were in line with the mean reference values (right, 19.8±6.9; left, 19.5±7.0) in the Turkish population in a previous study (7). Hence, our findings indicate the utility of the nasal Schirmer test in the objective evaluation of nasal humidity in patients with isotretinoin-treated acne vulgaris and the sensitivity of this test in discriminating the dose and treatment duration-dependent alteration in nasal dryness.

The association of 0.5 mg/kg daily dose of isotretinoin with an increase in mean VAS scores (1-3) after month 4 of treatment in our patients supports the data from previous studies indicated a significant increase in the mean VAS score of the patients from baseline (range: 0.1-2.7) to the end of isotretinoin treatment (range: 1.7-3.3) (4,14).

In a study by Tasli et al. (14) conducted with 54 patients with isotretinoin-treated acne vulgaris, authors reported a significant increase from baseline to months 1 and 3 of treatment in mean NOSE scores (14.04, 20.11, and 19.04, respectively), VAS scores (1.59, 2.14, and 2.21, respectively), and nasal dryness/crusting severity scores (0.47, 3.57, and 4.28, respectively) along with a significant increase in the percentage of patients with nasal dryness from 9.5% at baseline to 43% at month 3 of isotretinoin treatment.

In a study of 40 patients with acne vulgaris, Gorpelioglu et al. (12) revealed that the mean nasal MCT significantly increased after isotretinoin treatment along with a significant correlation between drug dose and prolonged nasal clearance. The authors also noted that nasal complications caused by isotretinoin, such as signs and symptoms of dry nose and disturbed mucociliary clearance, were mild in patients on the low-dose isotretinoin regimen (12).

In a study of 101 patients with isotretinoin-treated acne vulgaris, İşlek and Yıldız (4) reported significant increase from baseline values in MCT, NOSE, and nasal dryness VAS scores and indicated the role of routine ear-nose-throat control in patients with isotretinoin-treated acne vulgaris to timely recognize the potential adverse effects of the drug on the nasal mucosa (4).

While mucocutaneous dryness is suggested to cause crusting, increasing the likelihood of nasal passage obstruction and complaint of nasal obstruction (14), isotretinoin had no significant effect on pretreatment NOSE scores in the current study, and nasal obstruction was not reported as a significant problem by our patients, regardless of the dose and duration of isotretinoin treatment.

In the present study, a significant increase in VAS scores and a decrease in bilateral Schirmer values from baseline to months 2 and 4 of therapy were evident only in patients receiving 0.5 mg/kg daily dose of isotretinoin. Accordingly, given the dose dependency of side effects such as dry mouth, nasal dryness, and frequent nosebleeds, which are reported more frequently in the high-dose than in low-dose groups of patients who received isotretinoin, our findings appear to support the consideration of low-dose daily isotretinoin (0.25 mg/kg) regimen for 6 months as a logical treatment approach in patients with acne vulgaris (23). Indeed, several studies have reported that when considering tolerability, efficacy, and patient satisfaction, low-dose daily treatment (0.25-0.4 mg/kg) for a total period of 6 months is most suitable for patients with moderate acne (24-27).

Table 2. Study parameters in isotretinoin groups

	Pretreatment (n=102)		Month 2 (n=60)		Month 4 (n=46)		p ¹	
	0.25 mg/kg/day (n=35)	0.50 mg/kg/day (n=67)	0.25 mg/kg/day (n=21)	0.50 mg/kg/day (n=39)	0.25 mg/kg/day (n=14)	0.50 mg/kg/day (n=32)	0.25 mg/kg/day	0.50 mg/kg/day
VAS score								
mean ± SD	2±2	1±2	3±2	3±2***	4±2	3±3**	0.248	<0.001
median (min.-max.)	1 (0-7)	0 (0-5)	3 (0-7)	3 (0-7)	4 (0-7)	3 (0-9)		
p value ²	0.092		0.893		0.353		-	
NOSE score								
median (min.-max.)	0 (0-40)	0 (0-30)	0 (0-35)	0 (0-40)	5 (0-35)	0 (0-30)	0.098	0.882
p value ²	0.228		0.547		0.053		-	
Nasal Schirmer test								
Right Schirmer value								
mean ± SD	20±6	20±6	17±6*	17±6**	17±7	16±7**	0.008	0.001
median (min.-max.)	17 (13-35)	17 (10-35)	15 (9-34)	15 (10-35)	15 (7-30)	15 (4-35)		
p value ²	0.502		0.810		0.950		-	
Left Schirmer value								
mean ± SD	21±6	20±6	17±6	17±6**	15±6	17±8***	0.059	<0.001
median (min.-max.)	20 (12-35)	19 (9-35)	15 (10-30)	17 (7-30)	14 (10-30)	15 (5-35)		
p value ²	0.767		0.572		0.509		-	

VAS: Visual analog scale, NOSE: nose obstruction symptom evaluation, SD: standard deviation, min.: minimum, max.: maximum, ¹: Friedman test, ²: Mann-Whitney U test, *: p < 0.05, **: p < 0.01 and ***: p < 0.001; compared with pretreatment values (Wilcoxon test with Bonferroni correction, p < 0.016)

Study Limitations

First, the potential lack of generalizability appears to be an important limitation because of the relatively small sample size. Second, the short follow-up period and considerable loss to follow-up ratio also limited this study. Third, there was no data on epistaxis and mucociliary clearance, which otherwise could have extended the knowledge achieved in the present study.

Conclusion

Our findings revealed the association of isotretinoin treatment with nasal dryness but not with nasal obstruction in patients with acne vulgaris, particularly with the use of the high-dose (0.5 mg/kg) daily regimen, regardless of treatment duration. Our findings emphasize the utility of the nasal Schirmer test in the objective assessment of nasal dryness in patients who received isotretinoin treatment and the potential benefit of low-dose (0.25 mg/kg) isotretinoin regimen in reducing the risk of nasal dryness as a common etiological factor for eventual problems such as prolonged nasal clearance and epistaxis. Further larger-scale studies addressing the long-term nasal side effects of oral isotretinoin therapy are needed to develop optimal screening tools for the timely recognition, appropriate management, and follow-up of potential adverse effects of the drug on the nasal mucosa.

Ethics Committee Approval: The study was conducted following the ethical principles stated in the Declaration of Helsinki and approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 2501, date: 21/08/2020).

Informed Consent: Written informed consent was obtained from each patient.

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Authorship Contributions: Surgical and Medical Practices - E.Y.; Concept - E.Y., D.E., Z.Ç., E.C.; Design - E.Y., D.E., Z.Ç., E.C., Ö.Y.; Data Collection or Processing - E.Y., Z.Ç., E.C.; Analysis or Interpretation - E.Y., D.E., Z.Ç., Ö.Y.; Literature Search - E.Y., D.E., Z.Ç., E.C.; Writing - E.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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