Original Article / Çalışma - Araştırma

Effect of systemic isotretinoin treatment on voice

Sistemik isotretinoin kullanımının ses üzerindeki etkisi

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ABSTRACT

Objectives: This study aims to investigate the effects of oral systemic Isotretinoin (Iso) treatment of acne vulgaris, as a chronic inflammatory disease, on voice.

Patients and Methods: Between March 2014 and May 2016, a total of 62 volunteer patients (40 females, 22 males; mean age 22.4±5.5 years; range 18 to 36 years) with systemic Iso therapy indication due to acne vulgaris were included in the study. Ear nose and throat examination, videolaryngostroboscopy (VLS) and acoustic voice analysis (sound pressure level [SPL], mean F0, first three formants, jitter%, shimmer% and noise to harmonic ratio [NHR]) were performed, maximum phonation time (MPT) and s/z ratio were measured at pretreatment, third and sixth months of treatment and sixth month after the treatment was stopped. The Voice Handicap Index (VHI-10) and the GRBAS scales were performed for perceptual voice evaluation.

Results: There was no statistically significant difference in MPT, F0, the first three formants, SPL, GRBAS (increased during the treatment), shimmer% ratings and VLS parameters during the Iso treatment. Voice Handicap Index-10, s/z ratio, jitter% and NHR were observed to have increased significantly during the treatment.

Conclusion: Six-month regular systemic Iso treatment at standard clinical doses has mild negative effects on voice quality and this impact returns to baseline after the treatment is stopped. It is recommended that patients, especially vocal artists, to be informed prior to treatment about this possible side effect.

Keywords: Dysphonia; isotretinoin; voice.

ÖZ

Amaç: Bu çalışmada kronik bir inflamatuvar hastalık olan akne vulgarisin tedavisinde sistemik Isotretionoin (Iso) kullanımının ses üzerindeki etkisi araştırıldı.

Hastalar ve Yöntemler: Mart 2014 - Mayıs 2016 tarihleri arasında, akne vulgaris nedeniyle sistemik Iso kullanımı endikasyonu olan toplam 62 gönüllü hasta (40 kadın, 22 erkek; ort. yaş 22.4±5.5 yıl; dağılım 18-36 yıl) çalışmaya dahil edildi. Tedavi öncesinde, tedavinin üçüncü ve altıncı aylarında ve tedavinin bitiminden altı ay sonra kulak burun boğaz muayenesi, videolaringostroboskopi (VLS), akustik ses analizi (ses basınç seviyesi [SPL], ortalama F0, ilk üç formant, jitter%, shimmer% ve ses harmoni oranı [NHR]) yapıldı, maksimum fonasyon zamanı (MPT) ve s/z oranı ölçüldü. Algısal ses değerlendirilmesinde Ses Handikap İndeksi-10 (VHI-10) ve GRBAS kullanıldı.

Bulgular: Maksimum fonasyon zamanı, F0, ilk üç formant, SPL, GRBAS (tedavi sırasında artış gösterdi), shimmer% değerlerinde ve VLS parametrelerinde istatistiksel olarak anlamlı bir değişiklik saptanmadı. Ses Handikap İndeksi-10, s/z oranı, jitter% ve NHR'nin tedavi sırasında anlamlı olarak arttığı görüldü.

Sonuç: Standart klinik dozda altı aylık düzenli sistemik Iso tedavisinin ses kalitesi üzerinde hafif bir olumsuz etki gösterdiği ve bu etkinin tedavi sonlandırıldığında başlangıçtaki duruma döndüğü saptandı. Hastaların, özellikle de ses sanatçılarının, tedavi öncesinde bu olası yan etki açısından bilgilendirilmeleri önerilir.

Anahtar Sözcükler: Disfoni; isotretinoin; ses.

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Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit, characterized clinically by comedones, papules, pustules, nodules, cysts, sometimes scarring.[1,2] It is the most common dermatological disease of the young population. It can not lead to mortality but sometimes may lead to severe psycho-social morbidity and skin scarring among patients.[1] According to the type, severity, and distribution of lesions, topical and systemic agents (antibiotics, retinoids, and anti-androgens) are used for treatment.[2] Since the 1980's, oral isotretinoin (Iso) has been used in patients with severe acne vulgaris resistant to conventional treatments such as topical and systemic antibiotics.[2,3] Isotretinoin is a synthetic retinoid (13-cis-retinoic acid) that it affects many steps in acne pathophysiology.[3] Isotretinoin has been more preferred, even for less severe cases of acnes, because of its high efficacy, rapid effect and prolonged remission periods.[2,3]

The most commonly reported side effects of systemic Iso use are associated with its mucocutaneous toxicity.[4] Isotretinoin causes transepithelial water loss and also can affect sodium potassium adenosine triphosphatase channels and water channels in epithelial cells. Alterations of ion and water transport can affect the mucous layer and affect hydration of the underlying epidermis in a negative way and cause mucocutaneous dehydration.[5] Due to the these underlying mechanisms the main mucocutaneous side effects of Iso use in the head and neck region are; dryness of the skin, lips, mouth (xerostomia), nasal mucosa (epistaxis), cheilitis and inflammation and bleeding of the gums.[4,6] Even if it has not occurred yet, it has been postulated that the recognized side effects of Iso on mucosal surfaces and epithelium may emerge in the vocal folds (VF).

Vocal folds surface is covered by a thin layer of liquid (the mucous blanket, sol and gel layers). This layer serves as a physical and biochemical barrier that protects the VFs and plays an important role on healthy mucosal wave formation.[7] Favorable viscoelastic and vibratory capacity of the VFs is an essential part of optimal voice production. Alterations of this cover may affect vibratory function and cause dysphonia because it increases efficiency of VF oscillation and promotes normal voice quality.[8] All in all, potential VF mucosal dryness due to Iso therapy may hamper regular mucosal wave resulting in dysphonia. The aim of this study was to investigate the effects of Iso treatment on voice related parameters.

PATIENTS AND METHODS

This prospective single-blinded clinical study was carried out at the voice disorders unit of otorhinolaryngology and dermatology department at Yildirim Beyazit Research and Training Hospital between March 2014 and May 2016. It was approved by the research Ethics Committee of Yildirim Beyazit Research and Training Hospital (Decision number: 02.06.2014/16/28). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki. Subjects younger than 18 years of age who volunteered for this project were included. General exclusion criteria included; a history or evidence of oral neurotoxic drugs or corticosteroid intake, use of any vitamin A supplement, previous therapy with oral retinoids, alcohol misuse, metabolic, neurological, vascular or autoimmune diseases and any severe systemic disorder. Other exclusion criteria related to voice were as follows: history of smoking, intensive alcohol consumption, being a professional voice user, history of any respiratory, neurological, psychiatric or endocrinological diseases, laryngeal surgery, head and neck trauma, radiotherapy to the head and neck region, chemotherapy, hearing impairment, voice therapy, vocal training, any vocally abusive or misusive behaviors and any laryngopharyngeal reflux (LPR) complaint.

Patients began oral Iso therapy at daily doses of 0.6-1 mg/kg and titrated over six months to a cumulative dose of at least 120 mg/kg. Laboratory tests including blood count, liver enzymes and serum lipids, pregnancy test for women were performed before treatment and repeated monthly until completion of treatment. Main side effects of systemic Iso treatment mentioned in the literature before related to upper airway such as dryness of mouth and lips were also noted.

A total of 79 volunteer patients, fitting the defined criteria began the study. Iso treatment was ceased for nine of the 79 for the following reasons; four of them due to elevations in liver

function tests, two of them due to headache that could not be explained by any other reasons, two of them due to hypertriglyceridemia (>500 mg/dL) and in one of them due to general musculoskeletal pain. Eight patients did not come to the designated follow-up sessions. Therefore, the results expressed were for 40 women (mean age 21.7±5.8 years) and 22 men (mean age 22.6±5.3 years), a total of 62 patients, who completed the study properly.

The participants declared their voices to be normal. Medical and voice habituation history was obtained via a detailed questionnaire prepared for this study. Detailed ear, nose and throat and neurologic examinations were performed before, at the third month and sixth month of Iso treatment and sixth months after the treatment was completed. There were no signs of upper airway infection during any evaluation. Validated Turkish version of Voice Handicap Index-10 (VHI-10) was used for subjective self-reporting of severity of vocal symptoms. Voice Handicap Index-10 is composed of 10 questions. Subjects rate each question on a scale of 0-4. Increased scores refer to increased severity of the participants' problems.[9]

GRBAS scale was used for auditory-perceptual assessment of voice quality. This scale consists of 5 parameters (Grade, Roughness, Breathiness, Asthenia, Strain). Four scores from 0 to 3 is given according to the severity of evaluated parameter (0 is normal, 1 is slight, 2 is moderate, and 3 is high degree of severity).[10] Four experienced otolaryngologists, who did not know the patients, performed GRBAS separately on shuffled voice recordings of a reading Turkish paragraph with rich and balanced phonemes. The compatibility between evaluators was analyzed prior the study. The intraclass correlation coefficient for the inter-judge evaluation was statistically significant (83%, p=0.01).

If an individual's initial VHI-10 score was ≥2 with a mean GRBAS score ≥1, he/she was excluded.

Videolaryngostroboscopy (VLS) examination was performed (Xion Endo-Strob DX, Berlin, Germany) by the same otolaryngologist. The shuffled VLS recordings were evaluated and scored by two otolaryngologists together who did not know the subjects based on the protocol of the European Laryngological Society.[11] According to this protocol, the evaluated parameters are: Glottic closure, Regularity, Mucosal wave, and Symmetry. For each parameter, a four-point grading scale (0 no deviance and 3 severe deviance) was used. If any VLS parameter with score >1 was found, the subject was excluded.

Recording of voice samples was performed using a high-quality omnidirectional microphone (Shure SM48, Niles, US) in a sound insulated room. Computerized Speech Lab (Kay PENTAX CSL model 4500, Montvale, USA) software (CSL main program and MDVP) was used to

Table 1. Voice parameters of forty women at four different time points during isotretinoin therapy

	Postoperative therapy			
	Preoperative therapy	3th month	6th month	6th month
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Maximum phonation time (s)	15.2±2.3	15.5±2.1	15.5±1.7	14.9±3.1
S/Z ratio	0.86±0.12	1.01±0.23	1.34±0.33	0.88±0.11
Fundamental frequency 0 (Hz)	241.5±44.3	234.7±37.1	230.8±39.6	248.4±46.4
Fundamental frequency 1 (Hz)	896±77	872±68	874±74	878±66
Fundamental frequency 2 (Hz)	1896±185	1901±178	1887±182	1889±172
Fundamental frequency 3 (Hz)	2988±203	2991±198	2981±201	2979±194
Jitter%	0.61±0.32	1.20±0.33	1.47±0.39	0.64±.29
Shimmer%	2.68±0.84	2.85±0.86	2.86±0.84	2.76±.77
Noise to harmonic ratio	0.11±0.04	0.23±0.05	0.49±0.07	0.13±.03
Sound pressure level (dB)	62.7±3.8	61.0±3.5	60.2±4.5	64.4±5.0
Voice Handicap Index-10	0.45±0.26	3.92±1.02	5.14±1.79	0.53±0.31

SD: Standard deviation.

Table 2. Voice parameters of twenty-two men at four different time points during isotretinoin therapy

	Postoperative therapy			
	Preoperative therapy	3th month	6th month	6th month
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Maximum phonation time (s)	19.5±2.0	20.1±2.2	19.0±1.9	20.5±2.6
S/Z ratio	0.89±0.12	1.16±0.09	1.37±0.43	0.90±0.14
Fundamental frequency 0 (Hz)	129.0±24.8	125.8±13.8	121.7±22.2	126.0±23.7
Fundamental frequency 1 (Hz)	703.1±76.4	698.3±72.2	689.6±71.9	691.3±77.2
Fundamental frequency 2 (Hz)	1256±164	1251±172	1254±166	1261±158
Fundamental frequency 3 (Hz)	2432±169	2401±162	2426±173	2440±176
Jitter%	0.58±0.29	1.14±0.34	1.38±0.46	0.54±0.21
Shimmer%	2.54±0.72	2.52±.97	2.69±1.01	2.56±0.67
Noise to harmonic ratio	0.13±0.05	0.19±0.08	0.39±0.06	0.16±0.03
Sound pressure level (dB)	71.2±2.0	70.0±1.3	71.6±2.0	73.4±3.9
Voice Handicap Index-10	0.36±0.42	3.48±1.32	4.89±2.72	0.64±0.38

SD: Standard deviation.

capture and analyze the voice samples. After a short adaptation period to the procedure, subjects phonated sustained vowel [a] at a habitual pitch and comfortable level for at least seven seconds. Three recordings were captured for each patient, then the mean values were noted. To avoid involuntary irregularities on voicing onset and offset, two seconds (one at the beginning and the other one at the end) of voice samples were extracted. Analyzed acoustic parameters were: mean fundamental frequency (F0), the first three formant (F1, F2 and F3), sound pressure level (SPL), jitter percent (Jitt%), shimmer percent (Shim%) and noise to harmonic ratio (NHR). Maximum phonation time (MPT) was calculated as the duration of sustained vowel [a] after a maximum inhalation effort.

IBM-SPSS version 20.0 software was used for statistical analysis (IBM Corp., Armonk, NY, USA). The correlation analysis between variables was measured via Spearman's correlation test, and changes between different time periods among patients were evaluated using paired sample t-test. The numerical results were submitted as mean ±standard deviation. Statistical significance level was determined as $p<0.05$.

RESULTS

The voice parameters determined in the pre-treatment period, at the third and sixth month time points of the treatment and at sixth months after the treatment was stopped are summarized separately in Table 1 (female subjects) and Table 2 (male subjects). There was an increase for shimm% at the sixth month time point of the treatment compared to pre-treatment but it was not statistically significant. A statistically significant increase was determined for jitt%, NHR, s/z ratio and VHI-10 measures in the sixth month of treatment. These findings showed significant differences during the Iso treatment for all 62 patients. The VHI-10, s/z ratio, jitt% (refers to periodicity of frequency between glottal

Table 3. Significantly changed voice parameters of all sixty-two patients on pre- and sixth months of Iso treatment

	Preoperative Iso treatment	6th month of Iso treatment	
	Mean±SD	Mean±SD	*p*
Jitter%	0.59±0.030	1.44±0.36	0.001
Noise to harmonic ratio	0.12±0.02	0.45±0.04	0.000
S/Z ratio	0.87±0.13	1.36±0.33	0.03
Voice Handicap Index-10	0.42±0.61	5.04±1.48	0.000

SD: Standard deviation; There are not any statistically significant increase for any of these parameters between two periods.

Table 4. The main detected side effects of isotretinoin related to upper airway during treatment

	3th month		6th month	
	n	%	n	%
Dry and chapped lips	56	90.3	57	91.9
Dryness of the mouth	28	45.1	28	45.1
Dryness in the nose	16	25.8	19	30.6
Thirst	13	20.9	12	19.3
Nose bleeding	4	6.4	6	9.6
Difficulty in swallowing	3	4.8	4	6.4

cycles) and spectral parameter NHR (refers to noise in the voice signals) are submitted in Table 3 separately because these parameters are thought to not be affected by gender. Significant decrease was found for these four parameters six months after the treatment was stopped. There was no statistically significant difference for any of the voice parameters between pre and post-treatment sixth month evaluations.

Mean total GRBAS scores of pre-treatment, third and sixth month of treatment and sixth month after the treatment was stopped were respectively; 0.58±0.32, 0.73±0.45, 0.91±0.53 and 0.58±0.41. GRBAS scores of the third and sixth month time points of treatment were higher than the pre- and post-treatment evaluations but there was no statistically significant difference. There was no statistically significant difference for MPT, F0, F1, F3 and SPL values during the study. These parameters also showed neither increase nor decrease consistently during the study.

When evaluated separately there was no statistically significant change for the four different VLS parameters during the study. The total VLS evaluation score before treatment was 0.24±0.04. This score was determined as 0.31±0.06 on third month, as 0.38±0.09 on sixth month of treatment and 0.33±0.08 on sixth month after the end of the treatment and there was no statistically significant change during the study.

The main side effects of treatment related to upper airway reported by patients were dry-chapped lips and dryness of the mouth. The other side effects and their percentages are shown in Table 4.

DISCUSSION

The VFs' mobility characteristics are not only associated with simple adduction but also with their viscoelastic properties and pliability. Alterations in mass, viscosity, length, or tension of the VFs may cause abnormalities in the mucosal wave. Smooth and moist VF mucosal surface is required to maintain proper phonatory function. The mucus layer (sol layer, 10 μm in depth) which is a highly delicate structure on the surface of VFs is essential for healthy phonation.[12] It has been reported by Witt et al.[13] that superficial dehydration of the VFs may decrease the amplitude and frequency of the mucosal wave. The amount of energy distribution during vibration of VFs increases with viscosity; therefore, more aerodynamic energy is required to maintain the same phonatory status.[14] The influence of hydration level on voice quality was investigated by Verdolini-Marston et al.[15] They stated that viscosity is an important biomechanical property considering VF hydration and has a linear relationship with phonation threshold pressure.

Hemler et al.[16] suggested that stiffer and more viscous cover may cause some acoustic perturbation measures such as shimmer and jitter to deteriorate. This has been attributed to changes in biomechanical properties of mucosal wave. Similarly, our study suggests that the most common side effect of Iso treatment is mucocutaneous dryness of the lips and mouth and this side effect may hamper viscoelastic properties of VFs due to decreased lubricating secretions and cause dysregulation in mucosal wave pattern leading to the increase in s/z ratio, VHI-10, and some perturbation values. The increase in jitt% and NHR found in this study reflects the irregularity and increased noise within the glottal cycles. Worsening voice quality during Iso treatment in evaluations made by both patients (VHI-10) and listeners (GRBAS) is thought to be associated with this side effect of Iso.

At the six month of Iso treatment mean value for VHI-10 score was 5.04 (max 8) and mean GRBAS score was 0.91 (max 3). These results are lower than the mean total VHI-10 (>11 could be considered as abnormal) and GRBAS scores reported in the literature for patients with dysphonia. This decrease in perceived voice

quality is not at the same level of alterations found in patients with organic benign VF pathologies. In our study, Iso treatment did not cause severe perceptual voice problems in patients without any voice problems but its probable effects on patients with voice problems is not known.[17,18] Studies about the effects of Iso treatment on patients with voice problems are warranted. On the other hand, such alteration, though mild, may cause substantial problems in professional voice users. Thus, studies on this population are also required.

The lack of any significant alterations in MPT and SPL measurements may suggest that Iso does not cause changes in aerodynamic functions and/or glottal efficiency that may affect the voice. These results were compatible with VLS parameters which did not show any significant difference. Videolaryngostroboscopy related results of this study was thought to be related to limitation of stroboscopy. Because, VLS may not accurately reveal such minimal changes in mucosal wave, they may be induced by VF surface dehydration. In an experimental study, Li et al.[19] used digital videokymography and high speed imaging to assess surface dehydration level of VFs on mucosal wave parameters and they found that mucosal waves consistently decreased with increasing dehydration levels. Distinctive frequency components in the sound spectrum of voiced sound produced by resonating system are formants.[20]

The first three formant frequencies did not show any statistically significant alteration for either gender during the Iso treatment. This result suggests that even though the Iso treatment caused dryness of the mouth, lips, nose, and pharynx there were no alterations in vocal tract cross-sectional area.

Although it has numerous side effects, Iso treatment is well-tolerated and serious side effects of Iso are rare.[3,4] In our study nine patients (14.5%) left the study due to some side effects (elevated liver function tests, headache, hypertriglyceridemia and musculoskeletal pain). At the end of the six months of treatment, severe side effects were not reported in any of the included cases.

Absence of histopathological analyses of VF tissue samples was a limitation of this study. Some significant alterations in voice related parameters in this study does not mean that side effects were not present at ultrastructural VF level. Iso may alter ionic and osmotic composition of airway surface and underlying tissue liquid overlying the VF. This may also cause epithelial cell damage.[21] Studies examining tissue samples are required.

Consequently, the results of this study showed that a six-month peroral systemic Iso treatment at standard dosage may have mild voice disturbances. This probable mild unfavorable effect of Iso treatment is not thought to adversely affect the patients' quality of life. However this effect of Iso should be kept in mind when recommending this treatment for professional voice users, and also in patients who have organic VF problems. These results may be helpful in guiding both patients and clinicians about possible voice related side effects of this commonly used medicine.

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