Original Article / Çalışma - Araştırma

Evaluation of the clinical effects of isotretinoin on chronic rhinosinusitis

İsotretinoin kullanımının kronik rinosinüzit üzerindeki klinik etkilerinin değerlendirilmesi

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Objectives: This study aims to evaluate the clinical effects of isotretinoin (13-cis-retinoic acid), a derivative of retinoic acid, on the clinical features of chronic rhinosinusitis.

Patients and Methods: The study group included 25 chronic rhinosinusitis patients (16 females, 9 males; mean age 25.2±6.8 years; range 15 to 25 years) who were on isotretinoin for acne treatment, while the control group consisted of 25 chronic rhinosinusitis patients (15 females, 10 males; mean age 25.2±6.8 years; range 15 to 25 years) who were not on isotretinoin treatment. The patients' symptom scores in visual analog scale (VAS), Lanza and Kennedy nasal endoscopic scores and Newman computed tomography (CT) scores were obtained in order to evaluate the their symptom, examination and radiological findings. These patients' symptom and examination results were evaluated first day, week two and at months 3-5 and 6-10. Paranasal sinus CT results were studied first day and at months 6-10.

Results: In the group of patients being administered isotretinoin, no significant change in the mean symptom and examination scores was detected during the acute phase (week 2), while there was a significant regression in the long-term (months 3-5 and 6-10). There was a significant regression in the mean CT score after isotretinoin therapy. In the control group no significant change was seen in any of the scores. The number of acute sinusitis attacks were significantly lower in the isotretinoin group than in the control group. No significant difference was found between the two groups in terms of the duration of the healing period of acute sinusitis attacks.

Conclusion: We conclude that the long-term administration of isotretinoin has positive effects on the clinical results of chronic rhinosinusitis.

Key Words: Chronic rhinosinusitis; isotretinoin; medical treatment; retinoic acid.

Amaç: Bu çalışma, bir retinoik asit türevi olan izotretinoinin (13-cis-retinoik asit) kronik rinosinüzit kliniği üzerine olan etkilerini araştırmayı amaçlamaktadır.

Hastalar ve Yöntemler: Çalışma grubu, akne tedavisi için izotretinoin kullanmakta olan 25 kronik rinosinüzit hastası (16 kadın, 9 erkek; ort. yaş 25.2±6.8 yıl; dağılım 15-25 yıl), kontrol grubu ise izotretinoin kullanmayan 25 kronik rinosinüzit hastasından (15 kadın, 10 erkek; ort. yaş 25.2±6.8 yıl; dağılım 15-25 yıl) oluşturuldu. Hastaların semptom, muayene ve radyoloji bulgularının değerlendirilmesi amacıyla görsel analog ölçekteki (GAÖ) semptom skorları, Lanza ve Kennedy nazal endoskopi skorları ve Newman bilgisayarlı tomografi (BT) skorları elde edildi. Hastaların semptomları ve muayene bulguları birinci gün, ikinci hafta, 3-5 ve 6-10. aylarda değerlendirildi Paranazal sinüs BT sonuçları ise birinci gün ve 6-10. ayda çalışıldı.

Bulgular: İzotretinoin uygulanan gruptaki hastaların ortalama semptom ve muayene skorlarında akut dönemde (2. hafta) anlamlı bir değişiklik gözlenmez iken, uzun dönemde (3-5 ay ve 6-10 ay) anlamlı gerileme tespit edildi. İsotretinoin tedavisi sonrasında ortalama BT skorlarında anlamlı gerileme saptandı. Kontrol grubunda ise hiçbir skorda anlamlı bir değişiklik görülmedi. İzotretinoin grubunda akut sinüzit atakları kontrol grubuna göre anlamlı olarak daha az idi. Geçirilen akut sinüzit ataklarının iyileşme süreleri açısından iki grup arasında anlamlı bir fark tespit edilmedi.

Sonuç: Çalışmamızda izotretinoinin uzun dönem kullanımının rinosinüzite ilişkin klinik sonuçları üzerine olumlu etkileri olduğu sonucuna varıldı.

Anahtar Sözcükler: Kronik rinosinüzit, isotretinoin; medikal tedavi; retinoik asit.

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Rhinosinusitis is described as an inflammation of the nasal and paranasal sinus mucosa.[1] It is one of the most common epidemiological diseases ranking among the top ten diseases that cause productivity loss and increase the cost of treatment.[2] Anatomical stenosis of the ostiomeatal complex and anterior ethmoid area, pathologies in the structure of mucus and in ciliary activity are contributory to the pathophysiology of the disease.[3] Antibiotics, topical and systemic decongestants, mucolytics, topical and systemic corticosteroids and antihistamines are currently used in the medical treatment of rhinosinusitis.[4] However, there is need for new therapeutic agents because of the limited efficacy of these in chronic rhinosinusitis treatment.

Isotretinoin (13-cis-retinoic acid), a derivative of vitamin A is used for topical and systemic treatment of various dermatological diseases such as psoriasis, keratinization anomalies, keratotic genodermatosis and resistant acne.[5] Isotretinoin is the only agent that affects all the etiological factors in the pathogenesis of acne formation.[6] It affects cellular progression, differentiation and apoptosis, plays a role in reducing sebum production, hyperkeratinization (comedogenesis) and pilosebaceous unit surface and has anti-inflammatory effects.[7] Isotretinoin is known to have mucocutaneous and systemic toxic side effects. Despite these side effects, low dose isotretinoin administration (0.5-1 mg/kg/day) is safe and tolerable.[6]

The positive effects of vitamin A derivatives (retinoids) on respiratory and sensorineural epithelium (olfactory and auditory) proliferation are well known.[8] Studies pointing out the positive effects of retinoic acid (a derivative of vitamin A) on mucociliary activity are existing in the literature. Maccabee et al.[9] studied the effects of retinoic acid applied on surgically peeled-off maxillary sinus mucosa in a trial conducted on 12 New Zealand rabbits and observed better mucosal regeneration, less cellular atypia and fibrosis in the retinoic acid group. Hwang and Chan[10] reported higher levels of ciliary density, increase in orientation and morphology in the topical retinoic acid group in a study conducted with rabbit maxillary sinuses. Erickson et al.[11] by measuring the 'ciliary beat frequency' in rabbit sinus mucosa, showed that the use of topical retinoic acid increases ciliary regeneration. Although there are no studies examining the topical effects of vitamin A derivatives on human paranasal sinuses, systemic retinoid use decreases mucosal secretion by inhibiting glycoprotein synthesis.[12]

Based on these findings, we thought that retinoic acid may affect mucociliary activity disorders, mucosal congestion and inflammatory factors in rhinosinusitis pathogenesis by increasing mucociliary regeneration, decreasing mucosal secretion and through its anti-inflammatory effects. Therefore, we conducted a research studying the clinical effects of isotretinoin, a retinoic acid derivative, on rhinosinusitis. This is the first human study evaluating the effects of a retinoic acid derivate on chronic rhinosinusitis.

PATIENTS AND METHODS

This is a prospective, randomized controlled trial involving a total of 50 patients, aged 15 to 45 years who were diagnosed to have chronic rhinosinusitis and followed up from December 2008 to August 2010. The study group (n=25) was selected from among those patients (16 females, 9 males; mean age 25.2±6.8 years; range 15 to 25 years) already on isotretinoin treatment as indicated by the Dermatology Department. The control group (n=25) comprised chronic rhinosinusitis patients (15 females, 10 males; mean age 25.2±6.8 years; range 15 to 25 years) not using isotretinoin.

The diagnosis of chronic rhinosinusitis was based on 'Diagnosis Criteria of 1993 International Conference on Sinus Diseases' consisting of any one of the following:

- Rhinosinusitis symptoms and signs persisting for eight weeks
- A history of acute sinusitis attacks each lasting for a minimum of 10 days and recurring at least four times a year
- Persisting mucosal thickening on paranasal sinus computed tomography (CT) without acute sinus infection, despite four weeks of medical treatment.

Patients in the study and control group were informed about the objectives and nature of the trial and a consent form was collected. Patients on isotretinoin were followed up until they reached a total cumulative dose of 120-150 mg/kg. The patients were administered a daily dosage of 0.5-1 mg/kg and treatment was completed in 6 to 10 months.

Table 1. Age and sex distribution of patients

	Study group (n=25)				Control group (n=25)			
	Female		Male		Female		Male	
	n	%	n	%	n	%	n	%
Ages 15-25	8	32	5	20	7	28	5	20
Ages 26-35	5	20	3	12	5	20	3	12
Ages 36-45	3	12	1	4	3	12	2	8

Symptoms, physical examination, and paranasal sinus CT results were analyzed respectively using visual analog scale (VAS).[13] Lanza and Kennedy[3] nasal endoscopy score[14] and Newman CT scoring system.[15] Symptoms and examination results were evaluated at the start (first day) and during the acute phase (week 2), mid-treatment (months 3-5), and post-treatment (months 6-10) periods. Paranasal sinus CT results were obtained at the beginning and after treatment (months 6-10).

The fifty patients diagnosed to have chronic rhinosinusitis in both groups received the same standard treatment for each acute sinusitis exacerbation (daily doses of 2x1 gr amoxicillin clavulanate peroral (p.o) and 3x1 tablet pseudoephedrine-guaifenesin p.o for two weeks and oxymetazoline nasal spray 3x2 puffs for five days). The number of acute sinusitis exacerbations and the healing period of the patients were recorded and the group on isotretinoin treatment and the control group were compared according to these parameters.

The one sample Kolmogorov-Smirnov test was used to determine normal distribution, while Wilcoxon analysis was applied to determine the differences between the healing periods.

RESULTS

The age and sex distribution of the patients are given in table 1.

Patients on isotretinoin received a minimum of six and maximum of 10 months treatment with an average duration of 7.7±1.6 months. The minimum and maximum dosages were 20 mg and 40 mg respectively, with a mean of 30.4±7.3 mg.

The mean number of acute sinusitis exacerbations in the isotretinoin group was 2.2±0.7, while it was 3.7±1.1 in the control group. The mean healing period following an acute sinusitis exacerbation was 9.5±1.9 (days) for the group on isotretinoin treatment, while it was 11.1±3.1 (days) for the control group. There was a significant difference between the two groups in the number of acute sinusitis exacerbations (p=0.02), however no significant difference was seen in the mean healing period following acute sinusitis exacerbations (p=0.08).

There was no significant difference between the mean scores of VAS symptoms and Lanza-Kennedy[3] nasal endoscopy conducted at the beginning of the study and at week two for the isotretinoin group. There was a statistically significant difference in the mean of VAS symptom

Table 2. Comparison of symptoms, endoscopic examination and computed tomography scores in the study and control groups

	Pre-treatment	Week 2		Months 3-5		Months 6-10	
	Mean	Mean	*p*	Mean	*p*	Mean	*p*
Study group							
Visual analog scala score	4.05	4.01	0.057	2.80	<0.001	2.29	<0.001
Lanza and Kennedy score	0.86	0.81	0.053	0.38	<0.001	0.17	<0.001
Newman computed tomography score	1.31	–	–	–	–	0.78	<0.001
Control group							
Visual analog scala score	3.11	3.09	0.53	2.93	0.054	2.90	0.051
Lanza and Kennedy score	0.85	0.86	0.32	0.76	0.09	0.73	0.057
Newman computed tomography score	1.27	–	–	–	–	1.16	0.13

scores and Lanza-Kennedy[3] nasal endoscopy scores carried out in months 3-5 and 6-10 when compared to the outset values (table 2). There was a significant decrease in all symptom parameters and two of the examination findings (secretion and edema) during months 3-5 and 6-10 but no significant change was detected in the third examination finding (the polyp parameter; table 3).

There was no statistically significant difference in mean VAS symptom scores and mean Lanza-Kennedy[3] nasal endoscopy scores in the control group during the follow-up period (table 2). There was no significant change in any of the symptoms and examination parameters at week two, months 3-5 and 6-10 (table 4).

Paranasal sinus CT results were evaluated at first day and months 6-10. While there was a significant decrease in the chronic sinusitis findings in the mean Newman CT score in the study group, there was no significant difference within the control group. Bilateral maxillary, frontal, sphenoid and ethmoid sinus mucosal thickness and ostiomeatal complex obstruction parameters of the isotretinoin group displayed significant differences. No significant change was detected in the control group during the follow-up period (table 5).

DISCUSSION

Although antibiotics, topical and systemic decongestants and corticosteroids, mucolytics and antihistamines are administered to patients in the medical treatment of rhinosinusitis, these do not prevent the relapse of sinusitis attacks. As a result of recurring rhinosinusitis attacks, permanent mucosal damage occurs and chronic rhinosinusitis develops. The resulting chronic rhinosinusitis is more resistant to treatment and requires long-term medical treatment and/or surgical intervention. The search for novel methods in the treatment of rhinosinusitis is still ongoing because available medical treatment methods are not able to bring permanent cure. Hence, we studied the effects of isotretinoin on chronic rhinosinusitis.

Ünal et al.[16] in a rabbit study did not detect a significant difference in sinus mucosa inflammation and sinus epithelium integrity following administration of high doses of vitamin A in addition to antibiotic therapy in the treatment of acute sinusitis. We likewise found no significant effect of isotretinoin on the treatment of sinusitis during the acute phase (week 2; table 2).

We have established that after long-term use of isotretinoin treatment, a regression in all the symptoms, examination results (excluding polyps) and radiological results took place (tables 3 and 5) while there was no significant difference in any parameter in the control group (tables 4 and 5). Retinoic acid is known to increase mucociliary regeneration, decrease the amount of mucosal secretions and have anti-inflammatory, antioxidant and immunomodulatory effects.[9,12,17] We think that it may decrease mucociliary activity disorders, mucosal congestion and inflammation in sinusitis through the aforementioned effects.

Isotretinoin patients had significantly less exacerbations of acute sinusitis than the control

Table 3. Comparison of symptoms and endoscopic examination scores at week two, months 3-5 and 6-10 with basal values in the study group

	Pre-treatment	Week 2		Months 3-5		Months 6-10	
	Mean	Mean	*p*	Mean	*p*	Mean	*p*
Visual analog scale							
Nasal congestion	5.64	5.56	0.32	4.28	<0.001	3.36	<0.001
Dysnomia	2.72	2.72	1.00	1.92	<0.001	1.56	<0.001
Rhinorrhea	2.68	2.64	0.57	1.60	<0.001	1.16	<0.001
Postnasal discharge	5.44	5.40	0.32	3.48	<0.001	2.92	<0.001
Head and face ache	3.84	3.76	0.57	2.76	<0.001	2.48	<0.001
Lanza and Kennedy endoscopy score							
Secretion	1.20	0.12	0.16	0.60	<0.001	0.24	<0.001
Edema	1.12	1.04	0.16	0.36	<0.001	0.12	<0.001
Polyp	0.28	0.28	1.00	0.28	1.00	0.28	1.00

Table 4. Comparison of symptoms and endoscopic examination scores at week two, months 3-5 and 6-10 with basal values in the control group

	Pre-treatment	Week 2		Months 3-5		Months 6-10	
	Mean	Mean	*p*	Mean	*p*	Mean	*p*
Visual analog scale							
Nasal congestion	3.96	3.96	1.00	3.60	0.11	3.56	0.07
Dysnomia	2.64	2.56	0,32	2.52	0.37	2.40	0.11
Rhinorrhea	2.88	2.86	0.50	2.64	0.24	2.40	0.31
Postnasal discharge	3.08	3.04	0.32	2.88	0.13	2.72	0.06
Head and face ache	3.00	2.96	0.32	3.04	0.77	2.92	0.60
Lanza and Kennedy endoscopy score							
Secretion	1.04	1.08	0.32	0.88	0.21	0.88	0.21
Edema	1.20	1.20	1.00	1.08	0.26	1.00	0.09
Polyp	0.32	0.32	1.00	0.32	1.00	0.32	1.00

group during the follow-up period (p=0.02). The mean healing period for acute sinusitis exacerbations in the isotretinoin group was also shorter but no statistically significant difference was detected (p=0.08). Based on these results, we think that although this preparation has no effect on acute sinusitis, it may increase patients' quality of life in the long-term by decreasing exacerbations of acute sinusitis.

Isotretinoin treatment is known to have mucocutaneous and systemic toxic side effects. The mucocutaneous side effects are dose dependent and can usually be controlled with regular use of moisturizers and lip salves. Occasionally retinoid dermatitis (%65), cheilitis (%98) or conjunctivitis (%35) occur. Systemic side effects are uncommon and usually well controlled by dose reduction.[6] The patients in study group used a daily dosage

Table 5. Evaluation of pre-treatment and post-treatment paranasal computed tomography results of both groups

	Study group			Control group		
	Pre-treatment	Post-treatment	*p*	Pre-treatment	Post-treatment	*p*
Maxillary sinus mucosal thickness (mm)						
Right	1.96	1.28	<0.001	1.76	1.64	0.366
Left	1.52	0.80	<0.001	1.52	1.32	0.166
Frontal sinus mucosal thickness (mm)						
Right	1.28	0.76	<0.001	1.04	0.92	0.317
Left	0.80	0.24	<0.001	1.00	1.32	0.763
Ethmoid sinus mucosal thickness (mm)						
Right	1.40	0.76	<0.001	1.20	1.00	0.157
Left	1.08	0.40	<0.001	1.12	0.92	0.096
Sphenoidal sinus mucosal thickness (mm)						
Right	1.76	1.24	<0.001	1.08	0.92	0.132
Left	0.84	1.24	<0.001	1.28	1.08	0.132
Ostiomeatal complex obstruction (mm)						
Right	1.40	0.84	<0.001	1.36	1.32	0.739
Left	0.96	0.32	<0.001	1.36	1.24	0.336

of 0.5-1 mg/kg isotretinoin which is considered safe and tolerable.[6] Mucocutaneous side effects were seen in 23 of 25 patients and controlled with moisturizers. Systemic side effects were seen in four of 25 patients. One patient had liver function test elevation and two had lipid elevation. After treatment they rapidly returned to normal levels. One had myalgia and arthralgia without a change in bone mineral density level. No patient needed to stop drug usage because of the side effects.

We think that more objective data can be obtained by histopathological and ultrastructural analyses of sinonasal mucosa biopsies collected from patients receiving isotretinoin. And the results of our study should be supported by studies with a larger number of subjects.

We conclude that isotretinoin (13-cis-retinoic acid) has no significant effect on rhinosinusitis clinical findings during the acute phase but it decreases rhinosinusitis synptoms and signs significantly in the long term. This study demonstrates that long-term use of retinoic acid derivatives may form a strong therapeutic alternative in the medical treatment of chronic rhinosinusitis.

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