Original Investigation
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Assesment of acne vulgaris patients' attention tests during the isotretinoin treatment

Akne vulgarisli hastaların isotretinoin tedavisi sırasında dikkat ölçümlerinin değerlendirilmesi

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Abstract

Background and Design: This study aimed to investigate any relationship between an emerging attention deficit in patients with acne vulgaris and have reached cumulative doses under isotretinoin treatment.
Materials and Methods: A total of 100 patients (aged: 16-40 years) with acne vulgaris who have reached cumulative doses under isotretinoin medication for over a period of 6 months were included in the study. Using the Stroop Color and Word Test (SCWT), attention was assessed in the patients at the beginning and 3rd and 6th month of the treatment.
Results: A repeated measures ANOVA analysis was performed to determine whether there was any change in the SCWT results over time after the first dose and 3rd and 6th month of the treatment. The changes in all SCWT results were statistically significant with respect to time. The time required for each task assessed by means of the SCWT was found to be significantly reduced over time.
Conclusion: After evaluating the results of the SCWT performed at the beginning and 3rd and 6th month of the treatment, it was concluded that the treatment with the cumulative doses of isotretinoin was not significantly associated with any emerging attention deficit symptoms or signs in patients with acne vulgaris. It is possible that the patients were trained during the SCWT with the repeated performances in the study, which may have resulted a significant decrease in the test duration. This prospective study suggests that there is no casual relationship between the use of isotretinoin and attention deficit in patients with acne vulgaris.
Keywords: Isotretinoin, cumulative dose, Stroop test

Öz

Amaç: Çalışmada isotretinoin tedavisi başlanan ve kümülatif doza ulaşan hastalarda tedavi süresince ilaç kullanımı ile dikkat eksikliği arasındaki bir ilişkinin olup olmadığının tanımlanarak literatüre katkıda bulunması amaçlanmıştır.
Gereç ve Yöntem: Akne vulgaris tanısıyla isotretinoin tedavisi başlanan ve kümülatif doza ulaşan 16-40 yaş arası 100 hasta çalışmaya alınmıştır. Hastaların tedavinin başlangıcında, tedavinin 3. ayında ve 6. ayında Stroop testi ile dikkat ölçümleri (SCWT) değerlendirilmiştir.
Bulgular: Hastalara ilk başvurularında, tedavinin 3. ayında ve 6. ayında Stroop testi uygulanarak elde edilen SCWT ölçümlerinin zamana göre değişip değişmediğini belirlemek için tekrarlı ölçüm ANOVA analizi yapılmıştır. Stroop testine ait tüm ölçümlerin zamana göre değişimi istatistiksel olarak anlamlıdır. Her beş ölçüme ait sürelerin zamana göre anlamlı olarak azaldığı tespit edilmiştir.
Sonuç: İsotretionin başlanan kümülatif doza ulaşan hastaların tedavi başlangıcında, tedavinin 3. ayında ve 6. ayında yapılan Stroop testi sonuçları, isotretinoin tedavisi ile dikkat eksikliği arasında bir ilişkinin olmadığını testlerin okunma sürelerinde görülen anlamlı azalmanın, katılımcıların Stroop testini öğrenme etkisinden kaynaklanmış olabileceği düşünülmüştür. Bu prospektif çalışma, isotretinoin kullanımı ile dikkat eksikliği arasında nedensel bir bağlantı olmadığını göstermektedir.
Anahtar Kelimeler: İsotretinoin, kümülatif doz, Stroop testi

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Introduction

Affecting the major etiological factors in acne pathogenesis, isotretinoin has been indicated for the treatment of severe and treatment-resistant acne since it was approved by the Food and Drug Administration (FDA) in 1982; it is currently the preferred treatment regimen for this condition[1,2]. Four major mechanisms are involved in the pathogenesis of acne, including sebum production increase, ductal hyperkeratinization, microorganism colonization, and inflammation[3]. Despite being effective in the treatment of acne, discussions continue on the potential side effects of isotretinoin preparations related to the possible development of psychiatric disorders including affective disorders[4]. Depression, suicide, and suicidal ideation have been associated with the drug during the initial phase of its use[3]. However, in recent years, no mechanism of action or any causal relationship has been established between the use of isotretinoin and these psychiatric adverse effects[5]. Administration of isotretinoin has been associated with a 16% decrease in brain metabolism in the orbitofrontal cortex after 4 months of treatment[6]. Attention deficit and hyperreactivity disorder are due to the dysfunction of the frontal-subcortical cortex[7]. Decrease in the metabolism in the orbitofrontal cortex during the treatment with isotretinoin was thought to cause the frontal-subcortical cortex dysfunction, which is linked to the occurrence of attention deficit. Although the causal relationship between isotretinoin and mood changes has been extensively studied, data on the effects of the drug on attention are lacking. Based on this information, this study aimed to investigate the possibility of the occurrence of attention deficit due to the use of isotretinoin in patients with acne vulgaris.

Materials and Methods

This study was designed as a prospective study and was conducted from August 2017 to July 2018 in Düzce University Faculty of Medicine, Department of Dermatology after obtaining the approval of the Ethics Committee of the respective university and the faculty of medicine (approval number: 2017/99), Informed consent was obtained.

A total of 100 patients with moderate-to-severe acne were included in the study. The patients were excluded from the study if they were under the age of 16 or over 40 years of age, if they were previously diagnosed with an attention deficit disorder, depression, psychosis or anxiety disorder. One hundred and nine patients were included in the study, 100 of whom completed the study. The initial isotretinoin dosage was 0.3-0.5 mg/kg for the first month and then 1 mg/kg until a cumulative dose of 120-150 mg/kg had been completed.

Stroop task

The 5-card Stroop Color and Word Test (SCWT) was used for evaluating attention. The SCWT is a neuropsychological test extensively used for experimental and clinical purposes[8]. This test has been found to measure selective attention, cognitive flexibility information, and cognitive inhibition[9]. The following tasks were performed by the patients: reading the words on the card (1st card), reading the names of the colors written in different colored fonts (2nd card), identifying the colors of the colored circles (3rd card), identifying the colors of the words on the card (4th card), and identifying the colors in which the names of the colors were written on the card (5th card). The time required to complete each card task was assessed at the baseline before starting the treatment (I) and after the 3rd (II) and 6th (III) months of the treatment in the patients.

Statistical Analysis

Statistical evaluations were performed using the SPSS 21.0 IBM package program. Descriptive analysis methods were used in the evaluation of the sociodemographic data and the repeated measures ANOVA was applied to analyse the data obtained from the measurements collected at the different time periods during the study.

Results

The results of the Stroop test were evaluated, which was administered at three different time points (month 0, month 3, and month 6) to a total of 100 patients with acne vulgaris, who received isotretinoin for the treatment during the study. Of the participating patients in the study, 59% were females and 41% males. The mean age of the study patients was 23.84±5.5 years.

The Stroop color-word task was performed at the baseline before starting the treatmet, after three months, and after six months. The repeated measures ANOVA was conducted to determine whether the obtained results varied over the time. The results are presented in Table 1. Including reading the words on the card (1st card), reading the names of the colours written in different colour fonts (2nd card), telling the colours of the coloured circles (3rd card), telling the colours of the words on the card (4th card), and telling the names of the colours in which the colour names are written on the card (5th card) measurements showed statistically significant improvement with respect to time. The time spent by the patients during performing the tasks in each of the five cards were found to be significantly reduced over the time during the study. Significant difference between time groups were found for the 1st card when comparing I-II and II-III. Significant difference between time groups were found for the 2nd card when comparing I-III. Significant difference between time groups were found for the 3rd card when comparing I-III, II-III. Significant difference between time groups were found for the 4th card and 5th card when comparing I-II, I-III (Table 1).

Discussion

Although it has always been argued that a psychotropic effect can occur during the use of isotretinoin, studies conducted in recent years have consistently reported that there is no such relationship. Isotretinoin is a fat-soluble compound that can easily cross the blood-brain barrier. Intracellular retinoid receptors may interfere with the natural functioning of the central nervous system by affecting the dopaminergic-serotonergic system, hippocampal neurogenesis processes, and the frontal-orbital activity[4]. A study on positron emission tomography of patients with acne under isotretinoin medication showed decreased orbitofrontal cortical activity linked to the drug[10]. The regions of the brain vulnerable to the drug are determined as hippocampus and prefrontal cortex, which play a role in the mental order and coordination of cognition[11]. The most common psychiatric changes reported during the use of the drug are depression, psychosis, suicide or suicidal thoughts, mood swings, insomnia, and attention deficit[12].

Table 1. Time-dependent changes in Stroop Colour and Word test results

Stroop test	Sum of squares	df	Mean of squares	F	p	Significant difference between time groups
1st card	2.439	2	1.219	8.475***	0.000	I-II, II-III
2nd card	4.305	1.48	2.908	3.592*	0.043	I-III
3rd card	4.148	2	2.074	13.309***	0.000	I-III, II-III
4th card	5.984	1.43	4.160	5.497*	0.011	I-II, I-III
5th card	10.316	1.22	0.923	8.392**	0.002	I-II, I-III

I: The baseline before starting the treatment, II: After the 3rd months, III: After the 6th months
*p<0.05, **p<0.01, ***p<0.001

Azoulay et al.[13] conducted a study and reported that patients receiving isotretinoin tend to be 2.68 times more frequently depressed than individuals in the healthy population. In addition, it has previously been reported that between 1989 and 2003, of the 216 medication-related suicides by the individuals younger than 18 years old, 33% (72) were under isotretinoin medication[4]. This eventually led the FDA to include isotretinoin in the list of medications associated with depression. In 2003, this issue was included in the product label of the drug as a warning[12,14]. However, a meta-analysis of 31 studies by Huang and Cheng[15] found no association between isotretinoin and depression. Moreover, another side effect that may develop during isotretinoin use is attention deficit. To the best of our knowledge, except for the study conducted by Ergün et al.[16] and Botsali et al.[11], no other study evaluating attention deficit is available in the literature.

Acne is more frequently observed in patients during adolescence, when they continue their education. If isotretinoin is used as a treatment, any emerging symptoms or signs of attention deficit may impair the patients' performance in school. This potential untoward effect may also affect the business performance of the individuals who have professional life. An SCWT can be used to assess attention deficit. The SCWT is a neuropsychological test reflecting the activity of the frontal region of the brain. It is a reliable behavioral test, which was first developed by Stroop in 1935, used for the evaluation of experimental tasks. This preliminarily developed test formed the basis for the currently used SCWT and its various forms[17,18]. The SCWT reflects three main processes, including selective attention, reading, and naming the colors[19]. The SCWT results can be affected by clinical conditions such as dysarthria, mood disorders such as depression, and medication side effects[8]. In our study, the five cards of the test were used to assess attention. It was demonstrated that for each of the 100 patients included in the study, the time required to perform the tasks of the test significantly decreased over time, at all time points when the test was conducted, i.e., the beginning of the treatment and 3rd and 6th month of the treatment. Likewise, Ergün et al.[16] reported that in a 4-card SCWT on 48 patients[14], time required by all the patients to complete the tasks of the test during the treatment significantly improved. Furthermore, they reported that the other attention tests conducted in the study, like the visual memory test, showed no significant changes in the results over time. However, the time required to complete the letter fluency test improved over time. Botsali et al.[11], in their study on patients under isotretinoin medication, reported an improvement in the Stroop-TBAG form results and that the drug did not cause attention deficit. The present study suggested that the patients were trained in the SCWT due to the repeated performances in the study, which accounted for the significant decrease in the time required to perform the tasks. Therefore, the present study demonstrated that isotretinoin did not cause attention deficit in patients under medication for acne vulgaris.

Study Limitation

It could be done with other tests evaluating attention deficit.

Conclusion

The studies and meta-analyses conducted in recent years have indicated that the use of isotretinoin does not predispose patients to depression, suicide, or suicidal thoughts. However, there is a lack of data in the literature evaluating the association between isotretinoin and the emerging signs and symptoms of attention deficit. This prospective study suggested that there was no causal relationship between the use of isotretinoin and attention deficit in patients with acne vulgaris.

Ethics

Ethics Committee Approval: This study was designed as a prospective study and was conducted from August 2017 to July 2018 in Düzce University Faculty of Medicine, Department of Dermatology after obtaining the approval of the Ethics Committee of the respective university and the faculty of medicine (approval number: 2017/99).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

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References

1. Oliveria JM, Sobreira G, Velosa J, Telles Correia D, Filipe P: Association of isotretinoin with depression and suicide: A review of current literature. J Cutan Med Surg 2018;22:58-64.
2. Schaffer LC, Schaffer CB, Hunter S, Miller A: Psychiatric reactions to isotretinoin in patients with bipolar disorder. J Affect Disord 2010;122:306-8.
3. On SC, Zeicher J: Isotretinoin updates. Dermatol Ther 2013;26:377-9.
4. Hanna KJ, Agnieszka KP, Michal D, et al: Affective disorders as potential complications of anti-acne treatment with isotretinoin: A case series. J Affect Disord 2016;204:154-8.
5. Schrom K, Nagy T, Mostow E: Depression screening using health questionnaires in patients receiving oral isotretinoin for acne vulgaris. J Am Acad Dermatol 2016;75:237-9.
6. Bremner JD, McCaffery P. The neurobiology of retinoic acid in affective disorders. Prog Neuropsychopharmacol Biol Psychiatry 2008;32:315-31.
7. Voeller KK. Attention-deficit hyperactivity disorder. J Child Neurol 2004;19:798-814.
8. Scarpina F, Tagini S: The Stroop Colour and Word Test. Front Psychol 2017;8:557.

9. Rivera D, Morlett-Paredes A, PeñalverGuia AI, et al: Stroop Color-Word Interference Test: Normative data for Spanish-speaking pediatric population. NeuroRehabilitation 2017;41:605-16.
10. Bremner JD, Fani N, Ashraf A, et al: Functional brain imaging alterations in acne patients treated with isotretinoin. Am J Psychiatry 2005;162:983-91.
11. Botsali A, Kocyigit P Professor, Uran P: The Effects of isotretinoin on affective and cognitive functions are disparate in adolescent acne vulgaris patients. J Dermatolog Treat 2019;15:1-17.
12. Nevoralova Z, Dvorakova D: Mood changes, depression and suicide risk during isotretinoin treatment: A prospective study. Int J Dermatol 2013;52:163-8.
13. Azoulay L, Blais L, Koren G, LeLorier J, Berard A: Isotretinoin and the risk of depression in patients with acne vulgaris: A case-cross over study. J Clin Psychiatry 2008;69:526-32.
14. Barak Y, Wohl Y, Greenberg Y, et al: Affective psychosis following Accutane (isotretinoin) treatment. Int Clin Psychopharmacol 2005;20:39-41.
15. Huang YC, Cheng YC: Isotretinoin treatment for acne and risk of depression: A systematic review and meta-analysis. J Am Acad Dermatol 2017;76:1068-76.
16. Ergün T, Seckin D, Özaydın N, et al: Isotretinoin has no negative effect on attention, executive function and mood. J Eur Acad Dermatol Venereol 2012;26:431-9.
17. Stroop JR: Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:643-62.
18. Brugnolo A, De Carli F, Accardo J, et al: An updated Italian normative dataset for the Stroop Colour Word Test (SCWT). Neurol Sci 2016;37:365-72.
19. MacLeod CM: The Stroop task: The "gold standard" of attentional measures. J ExpPsychol Gen 1992;121:12-4.