Evaluation of Isotretinoin effects on depression, sleep apnea and sleep quality

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Abstract

Background

Isotretinoin is used to treat severe acne, treatment-resistant moderate acne and acne that leads to scarring or psychological distress. It has many side effects and is also associated with depression, sleep apnea and sleep disturbances.

Objectives

In this study, we aimed to evaluate the effects of isotretinoin on depression, sleep apnea and sleep quality.

Methods

A total of 42 patients diagnosed with acne and started isotretinoin treatment were included in the study. At baseline and after three months of treatment, patients filled out a questionnaire containing the Beck Depression Inventory (BDI), the Berlin Questionnaire (BQ) and the Pittsburg Sleep Quality Index (PSQI) in order to compare the effects of isotretinoin.

Results

There was no statistically significant difference in BDI, BQ and PSQI scores between week 0 and week 12 of treatment ($p = 0.53$, $p = 0.5$, $p = 0.035$).

Conclusion

This study showed no association between the use of isotretinoin and depression and sleep quality.

Introduction

Acne vulgaris is a chronic, inflammatory disease of the pilosebaseous unit. It is the most common skin disease, affecting 85% of adolescents [1]. Acne vulgaris can cause a wide range of psychiatric problems including anxiety, depression, social isolation, low self-esteem and even suicidal ideation [2].

Isotretinoin, an oral retinoid, has been used successfully since 1982 to treat severe acne, treatment-resistant moderate acne and acne that leads to scarring or psychological distress [3]. There are many reported side effects due to isotretinoin. The most common side effects are dryness of mucocutaneous membranes, headache, hyperlipidemia and musculoskeletal pain [4].

Vitamin A plays a role in cellular growth and differentiation and has important functions in the central nervous system [5,6]. In cases of vitamin A toxicity, symptoms such as aggression, depression, loss of concentration and psychotic symptoms have been reported [7,8]. As a vitamin A derivative, isotretinoin may also affect the central nervous system which may lead to psychiatric side effects (depression, behavioral disturbances, suicidality). On the contrary, some studies reported positive impacts on depression due to acne recovery, while others reported no association between isotretinoin and depression [9–12].

Sleep apnea has significant effects on sleep quality and causes excessive daytime sleepiness. There are individual safety reports of sleep apnea due to isotretinoin [13].

Delta oscillations in the electroencephalogram (EEG) refer to slow wave sleep is a parameter of assessing sleep depth and homeostatic need for sleep [14]. Maret et al. [15] reported that retinoic acid receptor affects delta oscillation in sleep EEG of mice. This result suggests that retinoic acids may affect sleep functions. There are few cases of sleep disturbances reported in patients treated with isotretinoin [16–18].

In this study, we aimed to evaluate the relationship between isotretinoin and depression, sleep apnea and sleep quality.

Material and Methods

A total of 42 patients diagnosed with acne vulgaris and started isotretinoin were included in the study. Exclusion criteria were the presence of systemic diseases, having a BMI ≥ 30, having depression or other psychiatric disorders, sleeping disorders and sleep apnea. The local ethics committee approved the study (E-20, 214). All participants were informed about the study and their written consent form was obtained.

The acne severity of the patients was calculated according to the global acne scoring system [19] and classified as mild (1–18 points), moderate (19–30 points) and severe acne (≥ 31 points). The demographic characteristics of the patients; such as age, sex and BMI were recorded. The place of residence of the patients was also recorded. The total dose of isotretinoin at the end of 12 weeks was calculated.

The patients were asked to fill out a questionnaire containing the Beck Depression Inventory (BDI), the Berlin Questionnaire (BQ) and the Pittsburg Sleep Quality Index (PSQI) at the beginning and 12 weeks of treatment.

BDI is a 21-item self-report questionnaire developed to measure depressive symptoms [20]. Each question is scored between 0–3 points and total score is calculated. The total score is categorized as no or minimal depression (> 10 points), mild depression (10–18 points), moderate depression (19–29 points) and severe depression (30 < points).

BQ is designed to screen for obstructive sleep apnea (OSA). It contains three sections; the first section evaluates snoring, the second section evaluates daytime sleepiness and the third section investigates

history of hypertension and obesity. At the end of the questionnaire, each section is evaluated within itself. Tests that show 2 or more positive section, are considered to have high risk for OSA [21].

PSQI is designed to assess sleep quality. It contains 19 self-reported items divided into seven subcategories which evaluate sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. There is an additional section for the roommate or bed partner of the filler to answer which is not included in the total score. A score of 5 or greater indicates poor sleep quality [22].

The scores of BDI, BQ, and PSQI were calculated and compared at baseline and 12 weeks of isotretinoin treatment.

Statistical Analysis

Descriptive statistics were analyzed in IBM SPSS 22.0 program. Shapiro-Wilk test was applied to reveal whether the data were suitable for normal distribution. The t-test was used to compare the means of two independent groups in a normal distribution. Pearson correlation analysis was used to determine whether there is a linear relationship between two numerical measurements, and if so, what is the direction and severity of this relationship. The statistical significance was accepted as $p < 0.05$ for this study.

Results

A total of 42 patients were included in this study. Of the 42 patients, 14 (33.3%) were male and 28 (66.7%) were female. The mean age was 20.47 ± 4.01. The mean BMI of the patients was 22.08. All patients were living at home with their families except for one patient was living in the dormitory. Two (4.8%) of the patients had mild acne, 21 (50%) had moderate acne and 19 (45.2%) had severe acne. The mean total dose of isotretinoin was 2911 milligrams (mg) at the end of the 12 week treatment. The mean time of sleep was 8 hours 4 minutes per day (Table-1).

All patients were evaluated with BDI questionnaire before treatment and 18 (42.9%) of the patients had no-minimal depression, 13 (31%) had mild, 3(7.1%) had moderate and 8 (19%) had severe depression. At the end of 12 weeks of treatment; 20 (47.6%) of the patients had no-minimal depression, 11 (26.2%) had mild depression, 8 (19%) had moderate depression and 3 (7.1%) had severe depression. The overall BDI scores were found to be decreasing compared to the baseline. However, it had no statistically significant difference ($p = 0.53$).

There was no statistically significant difference between the baseline and 12 weeks of treatment in terms of total and three subgroup scores of BQ ($p = 0.5$, $p = 0.52$, $p = 0.62$, $p = 1$).

No statistically significant difference was found in PSQI scores between baseline and 12 weeks of treatment ($p = 0.035$) and also between PSQI subgroups ($p = 0.55$, $p = 0.42$, $p = 0.89$, $p = 0.4$, $p = 0.4$, $p = 1$, $p = 0.3$). At the baseline 23 patients and at 12 weeks of treatment 29 patients were found to have a total

score of PSQI ≥ 5. However, there was no statistically significant difference between baseline and 12 weeks of treatment. when compared with the baseline. (p = 0.17), (Table-2).

Discussion

Isotretinoin is used to treat severe acne, treatment-resistant acne and acne that causes scarring or psychological distress [3]. There are many side-effects reported due to isotretinoin. However, some of the side-effects are not fully associated with isotretinoin and not fully evaluated with studies.

Physiological impacts of acne vulgaris are well documented. In many studies, having acne alone is related to higher rate of depression than the acne-free control group [23,24]. However, the relationship between isotretinoin use and depression is controversial. According to Oliveira et al.'s meta-analytic research [25], the association between isotretinoin and depression was mainly reported in case reports and retrospective studies. In contrast, prospective studies showed no association between isotretinoin use and depression [9, 10, 26–29]. This result can be explained by the differences between the designs of the studies. For example, prospective studies, usually exclude patients with a personal or family history of psychiatric disease from the study; which may have led to lower depression rates associated with isotretinoin. Some studies reported improvement of depressive symptoms in acne patients after treatment with isotretinoin [9–12, 30–32]. This result may be related to the improvement in self-image provided by the regression of acne lesions. There are also studies used BDI to evaluate the effects of isotretinoin on depression and found statistically significant positive effects [9,27,31]. We found no association between the use of isotretinoin and depression. On the contrary, depression scores had decreased after treatment with no statistically significant difference.

Sleep apnea is characterized by airway obstruction that leads to nocturnal hypoxemia. Sleep apnea has significant effects on sleep quality and excessive daytime sleepiness is one of the main symptoms of sleep apnea. According to Individual safety reports, 106 patients reported sleep apnea among the 168.235 side effects due to isotretinoin treatment. This rate was found to be higher than other drugs. Similarly, isotretinoin reported sleep apnea (100 among 150.424 side effects) found to be higher than other acne treatments (1 among 210.104 side effects) [13]. In our study, none of the patients had high risk for sleep apnea before and after 12 weeks of isotretinoin treatment. However, patients with comorbidities such as hypertension and obesity were excluded from the study, therefore the last section of the BQ was negative in all patients. Overall, in this study we found no association between isotretinoin and sleep apnea. To our knowledge, this is the first prospective study that evaluates the association between isotretinoin treatment and sleep apnea.

Isotretinoin passes the blood-brain barrier and has effects on the dopaminergic, cholinergic and serotonergic neurotransmission which is considered the mechanism of isotretinoin on sleep. However, different cases of sleep disorders (both hypersomnia and insomnia) with different mechanisms reported with isotretinoin use. Therefore, it is difficult to detect the pathogenesis of isotretinoin in the CNS that causes sleep disorders.

The effects of isotretinoin on sleep is a topic that is not fully researched. There are only a few cases of sleep disturbances reported in patients using isotretinoin [15,16,35].

Gupta et al. [15], reported sustained dreaming in two patients on isotretinoin which subsided spontaneously after a period of time without the need to discontinue isotretinoin. Dreaming is closely related to rapid eye movement (REM) sleep. Due to an increase in cholinergic activity in the CNS, isotretinoin may lengthen the duration of REM sleep. This may have led to persistent dreaming.

One case of hypersomnia and depression in a patient after 3 days of isotretinoin treatment and one case of hypersomnia after 2–3 weeks of treatment were reported [16]. Hypersomnolence has also been reported as one of the symptoms in cases of vitamin A toxicity [7]. In a study, after a four-week vitamin A deficiency diet, mice EEG showed a decreased delta wave in non-rapid eye movement (NREM) state, but not in the REM and wake states, compared to the control group. Moreover, the circadian rhythm was not affected by the vitamin A deficiency diet [33].

There are also reported cases of insomnia induced by isotretinoin. The US Food and Drug Administration (FDA) adverse event reporting system has extracted 1095 cases of insomnia related to isotretinoin out of 218,594 adverse effects. This correlation between isotretinoin and insomnia was found to be significant compared to other acne treatments [34]. Assiri et al. [35], reported a patient who had severe insomnia after six months of isotretinoin treatment, which insomnia recovered after dose reduction.

Ismailogulları et al.[36], performed polysomnography (PSG) on patients before and after one month of isotretinoin treatment. They reported increased sleep efficiency without effects on sleep stage and daytime sleepiness. Delta wave in slow wave sleep (a state of NREM sleep) decreased insignificantly. No increase in sleepiness was detected in the Epworth sleepiness scale. These results were not consistent with the hypothesis that isotretinoin increases delta waves in slow wave sleep. Moreover, the increase in sleep efficiency was interpreted as a ‘first-night effect’, in which the patients slept well the second time because of familiarity with the procedure.

In our study, the PSQI score increased by 0.55 points after 3 months of treatment, with no statistically significant difference. While evaluating PSQI subgroups; from the questions that access sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, and daytime dysfunction higher scores were obtained, but there were no statistically significant differences in any subgroup between week 0 and week 12 of the treatment. Overall, we could not reveal any effect of isotretinoin on sleep. Although one of the patient self-reported that he was asleep yet his mind wasn't fully closed. We interpreted this state as an idiosyncratic reaction.

The limitations of the study were small number of study group, the lack of a control group to compare the subjects and the fact that we only assessed the patients with questionnaires and did not perform further examinations (psychiatric examination, PSG).

Conclusion

This study showed no association between isotretinoin and depression, sleep apnea or sleep quality. The literature contains only case reports of sleep disturbances due to isotretinoin treatment and a study in a small group of patients. Further studies with larger sample groups and with more objective examinations are needed to reveal the effects of isotretinoin on sleep.

Declarations

Conflict of interest: There are no financial conflicts of interest to disclose.

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Tables

Table-1: Characteristics of patients

	Patient (n=42)
Age, mean (year)± Std	20.47±4.01
Gender, n(%)	
Male	14 (33.3)
Female	28 (66.7)
BMI, mean (kg/m^2)	22.08
Acne severity classification, n(%)	
Mild	2 (4.8)
Moderate	21 (50)
Severe	19 (45.2)
Isotretinoin dose, mean (mg)	2911
Sleeping time, hour	8.04

Std: Standard deviation, BMI: Body mass index, mg: miligram

Table-2: Comparison of scoring systems between week 0 and week 12

Scoring systems	Week 0	Week 12	P value
Beck score, mean	13.9	12.3	0.53*
Beck score classifications, n(%)			0.18**
No or minimal depression (>10 points)	18 (42.9)	20 (47.6)	
Mild depression (10-18 points)	13 (31)	11 (26.2)	
Moderate depression (19-29 points)	3 (7.1)	8 (19)	
Severe depression (30< points)	8 (19)	3 (7.1)	
Berlin score, mean	0.95	1.09	0.5
Berlin 1	0.09	0.16	0.52*
Berlin 2	0.83	0.92	0.62*
Berlin 3	0.02	0.02	1*
Pitssburg score, mean	5,42	5,97	0.35*
Sleep quality	1.16	1.09	0.55*
Sleep latency	1.14	1.3	0.42*
Sleep duration	0.66	0.69	0.89*
Habitual sleep efficiency	0.47	0.61	0.4*
Sleep disturbances	1.21	1.3	0.4*
Use of sleeping medication	0.2	0.2	1*
Daytime dysfunction	0.73	0.92	0.3*
Pitssburg score classifications, n(%)			0.17**
Score of < 5	19 (45.2)	13 (31)	
Score of ≥ 5	23 (54.8)	29 (69)	

*: T test **: Chi-square