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Effect of isotretinoin use on hematological parameters and biochemical values

Yalçın Karagöz[1], Mustafa Tosun[2]
[1] Department of Health Management, Business Faculty, Düzce University, Düzce
[2] Department of Dermatology, Medicine Faculty, Sivas Cumhuriyet University, Sivas, Turkey

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Abstract
Aim: The aim of this study was to investigate the general effects of oral isotretinoin on hematological parameters and biochemical values, and to identify whether these values vary according to age and gender.
Material and Methods: The study included 143 patients diagnosed with moderate or severe acne in the age range of 15-47 years. Patients were monitored retrospectively. Hematological parameters and biochemical values were recorded before treatment, then at the end of the first and third months of the treatment.
Results: The serum lipid levels, creatinine, cholesterol, triglyceride and AST values of liver enzymes, and renal function values were found to increase after the onset of treatment. Hematological parameters including LYM, HGB, HCT, RDW, MCV, PLT, MPV and PCT parameters were seen to increase after the onset of treatment, while the NEU parameter decreased. The values of other hematological parameters did not change.
Discussion: Although the use of oral isotretinoin has been shown to cause changes in hematological parameters and serum lipid levels, liver and renal function values, these changes usually remain within normal limits and continue with treatment.

Keywords
Isotretinoin, Acne, Hematological Parameters, Biochemical Values

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Corresponding Author: Mustafa Tosun, Dermatology Department, School of Medicine, Sivas Cumhuriyet University, 58140, Sivas, Turkey.
E-mail: mustafatosun@cumhuriyet.edu.tr P: +90 544 607 29 16
Corresponding Author ORCID ID: https://orcid.org/0000-0002-6189-8016

Introduction

Acne vulgaris is a chronic inflammatory dermatological disease, which is more prevalent during adolescence and has a significant psychological effect on patients. It is a widespread condition during adolescence with a prevalence of approximately 85% [1]. Oral isotretinoin is a highly effective treatment method, which is widely used in acne treatment. Increased sebum production, altered keratinization, inflammation, and bacterial colonization are involved in the etiology of acne. Oral isotretinoin is the only drug that can affect these four pathogenic factors involved in the etiology of acne. It is known that oral isotretinoin reduces sebum secretion by decreasing sebocyte proliferation and differentiation and minimizing sebaceous gland size. It ameliorates follicular keratinisation and prevents follicular plug formation. It decreases the number of propionibacterium acnes and inflammation, thereby treating acne [2]. Oral isotretinoin is used in the treatment of acne that causes scarring and in the treatment of nodulocystic moderate to severe acne that does not respond to other systemic antibiotics and topical treatments.

Oral isotretinoin is a very effective treatment, although there are some side effects, including cheilitis, xerosis, conjunctivitis, xerophthalmia, nosebleeding, photosensitivity, elevated serum lipid levels (especially triglyceride and cholesterol), pancreatitis, hyperostosis, elevated liver enzyme levels, and teratogenicity [3].

The use of oral isotretinoin in the treatment of moderate to severe cystic acne was first approved by the Food and Drug Administration (FDA) in 1982. Serum lipid levels and liver enzymes of patients using oral isotretinoin are monitored by monthly blood testing, for which there is no generally accepted procedure. Moreover, there is no standard practice on how often these levels should be tested (weekly, monthly or bi-monthly), and which parameters (i.e. cholesterol, triglycerides, complete blood cell counts) should be considered [4]. This situation can lead to unnecessary financial expenses and cause unnecessary invasive procedures for patients. The aim of this study was to determine whether there is any significant difference in the specified parameters of patients before and during isotretinoin treatment. It was also aimed to determine the presence of a statistically significant difference in the parameters of the patients according to their age and gender.

Material and Methods

Before the study began, the necessary approval was received from the local ethics committee of our hospital dated 30/07/2018 and 2018-07/11 numbered decision, in accordance with the Patient Rights Regulation and ethical principles.

The study included 143 patients with moderate or severe acne vulgaris who were admitted to the Dermatology Clinic of Sivas Numune Hospital and started to receive oral isotretinoin treatment. Their medical records were retrospectively reviewed. Hematological parameters and biochemical values of the patients were compared before treatment, then at the end of the first and third months of treatment. These patients received 0.5-1 mg/kg of isotretinoin treatment. Patients with any liver disease, active infection, or hematological disease were not included in the study. The white blood cell (WBC), neutrophil (NEU), eosinophil (EOS), lymphocyte (LYM), basophil (BASO), monocyte (MONO), and red blood cell (RBC) counts, hemoglobin (HGB), hematocrit (HCT), aspartate aminotransferase (AST), red cell distribution width (RDW), mean corpuscular volume (MCV), platelet (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), creatinine, cholesterol, triglyceride, and alanine aminotransferase (ALT) levels, and the neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) values were evaluated.

The data obtained in the study were analyzed statistically using SPSS 23 software, licensed by Cumhuriyet University (Authorization Code: e56444b2255bd0030cf1). Parametric statistical tests were used since the data conformed to normal distribution. The Repeated- Measures ANOVA test was used to analyze the variables obtained from consecutive measurements made at three different time points. When the significance (p) value of Mauchly's Test of Sphericity test was >0.05, the results of the Sphericity Assumed test were interpreted because the sphericity hypothesis was supported. When the significance (p) value of the Mauchly's Test of Sphericity test was <0.05, the results of the Greenhouse-Geisser test were interpreted because the sphericity hypothesis was not supported.

Results

The study included a total of 143 patients (94 females, 49 males) with moderate or severe acne vulgaris, aged 15-47 years. From the analysis, it was examined whether there was a significant difference between the consecutive data obtained at three different time points and whether there were differences in terms of gender and age at these times. A significance level

Table 1. The differences between the variables in measurements performed at three consecutive times

Variable	Before treatment	First month of treatment	Third month of treatment	P Value
	Mean ± SD	Mean ± SD	Mean ± SD	
WBC	7,903±0,177	7,729±0,165	7,608±0,161	0,223
NEU	4,719±0,137	4,435±0,145	4,320±0,132	0,022*
EOS	0,141±0,012	0,138±0,010	0,140±0,008	0,959
LYM	2,385±0,051	2,494±0,062	2,534±0,055	0,008*
BASO	0,032±0,002	0,029±0,002	0,031±0,002	0,26
MONO	0,573±0,014	0,591±0,016	0,581±0,014	0,478
RBC	5,072±0,043	5,108±0,043	5,093±0,044	0,176
HGB	14,224±0,142	14,333±0,146	14,378±0,143	0,014*
HCT	42,664±0,385	42,972±0,389	43,240±0,362	0,012*
MCV	84,206±0,385	84,175±0,396	84,954±0,385	0,001*
RDW	13,164±0,098	13,089±0,101	13,295±0,115	0,013*
PLT	285,187±6,291	298,403±5,944	295,806±6,254	0,002*
MPV	10,013±0,094	10,032±0,091	10,059±0,087	0,717
PDW	11,878±0,155	11,946±0,155	11,724±0,155	0,09
PCT	0,286±0,006	0,298±0,006	0,295±0,006	0,005*
NLR	3,920±1,841	3,480±1,559	3,119±1,341	0,121
PLR	125,051±3,079	126,790±3,339	121,976±3,234	0,258
Creatinine	0,755±0,012	0,770±0,013	0,785±0,013	0,000*
Cholesterol	149,846±2,528	162,438±2,678	166,293±2,829	0,000*
Triglyceride	98,134±4,485	118,341±5,110	111,691±4,676	0,000*
AST	17,349±0,433	19,590±0,336	19,241±0,302	0,000*
ALT	15,348±0,963	15,360±0,623	14,527±0,504	0,455

*p<0.05

Table 2. The differences between the variables in measurements performed at three consecutive times in terms of gender

Variable	Gender	Before treatment	First month of treatment	Third month of treatment	P Value
		Mean ± SD	Mean ± SD	Mean ± SD	
LYM	Female	2,343±0,063	2,519±0,077	2,610±0,067	0,003*
	Male	2,466±0,087	2,447±0,106	2,388±0,092	
PLT	Female	293,477±7,694	310,352±7,146	313,045±7,310	0,006*
	Male	269,326±10,642	275,543±9,883	262,826±10,111	
PCT	Female	0,296±0,008	0,312±0,007	0,314±0,007	0,010*
	Male	0,265±0,010	0,271±0,010	0,258±0,009	
Creatinine	Female	0,686±0,011	0,688±0,011	0,706±0,011	0,049*
	Male	0,890±0,016	0,929±0,016	0,941±0,016	
Cholesterole	Female	151,592±3,103	165,308±3,271	171,035±3,412	0,037*
	Male	146,391±4,364	156,761±4,600	156,911±4,799	

*p<0.05

Table 3. The differences between the variables in measurements performed at three consecutive times in terms of age

Variable	Age	Before treatment	First month of treatment	Third month of treatment	P Value
		Mean ± SD	Mean ± SD	Mean ± SD	
PCT	18 and under	0,275±0,011	0,292±0,011	0,281±0,010	0,036*
	19-21	0,306±0,010	0,306±0,010	0,306±0,009	
	22 and over	0,270±0,011	0,293±0,011	0,294±0,011	

*p<0.05

of 5% was considered to evaluate the results of the analysis.

According to the results of the Repeated Measures ANOVA test shown in Table 1, oral isotretinoin did not make a significant difference in WBC, EOS, BASO, PDV, NLR, PLR and ALT values. A statistically significant difference was determined in the hematological parameters of NEU, LYM, HGB, HCT, MCV, RDW, PLT, PCT and in the biochemical values of creatinine, cholesterol, triglyceride and AST.

The mean NEU values were found to be decreased compared to the baseline as the treatment procedure progressed. The mean values of LYM, HGB, HCT, creatinine and cholesterol were found to be increased compared to the baseline as the treatment procedure progressed. The mean MCV and RDW values were found to be decreased in the first month and increased in the third month compared to the baseline. The mean values of PLT, PCT, triglyceride and AST were found to be increased in the first and third months compared to the baseline, and decreased at 3 months compared to the first month.

According to the results of the Repeated Measures ANOVA test shown in Table 2, oral isotretinoin did not have a significant effect in terms of gender on the values of WBC, NEU, EOS, BASO, MONO, RBC, HGB, HCT, MCV, RDW, MPV, PDW, NLR, PLR, triglyceride, AST and ALT. A statistically significant difference was determined in the hematological parameters of LYM, PLT, PCT and biochemical values of creatinine and cholesterol.

When the mean values of LYM were evaluated, it was seen that the values in females increased compared to the baseline while those of males decreased. When the mean PLT and PCT values were examined, the values in females increased compared to the baseline, while the values of the males increased in the first month and decreased in the third month. The mean values of creatinine and cholesterol in both males and females increased in comparison to the baseline.

According to the results of the Repeated Measures ANOVA test shown in Table 3, with the exception of PCT, oral isotretinoin did not significantly affect all biochemical values and hematological parameters in terms of age.

The mean values of PCT in the age group ≤18 years old initially increased in the first and the third months compared to the baseline and decreased in the third month compared to the first month. The mean values of PCT in the age group 19-21 did not differ compared to the baseline. The mean values of PCT for the age group ≥22 years did not differ in the first month and increased in the third month compared to baseline.

Discussion

Systemic isotretinoin (13-cis retinoic acid), a vitamin A derivative, is an effective method in the treatment of moderate to severe acne, which does not respond to other treatments. It affects all the etiological factors of acne. It provides cell cyclus progression, cellular differentiation and apoptosis. It reduces sebum production and affects comedones. It reduces Propionibacterium acnes and has anti-inflammatory properties [5, 6].

However, oral isotretinoin may cause several side effects. The most critical side effect is teratogenicity. Other side-effects are dry lips, cheilitis, conjunctivitis, xerosis and biochemical changes (transaminase, triglyceride, cholesterol etc.), respectively [7]. The most commonly observed laboratory changes reported in the literature are high serum lipid and hepatic enzymes levels. In this study, cholesterol, triglyceride and AST values were found to be statistically significantly high in the third month of treatment compared to pre-treatment. There was also a statistically significant increase in creatinine values. The difference in cholesterol and creatinine values in females was found to be higher than in males. Similar results were reported by Ataseven et al. (2013) with high levels determined of cholesterol and triglyceride and no change observed in creatinine values [8]. In the current study, a significant increase in PCT values was also determined in the age groups under 18 years and over 22 years.

In a study by Alcalay et al. (2001), liver enzymes were not found to be high enough to cease treatment, only 1.5% of patients had high serum triglycerides, and no routine laboratory procedure

was required in younger people [9]. In another study, it was suggested that laboratory values of patients with serum lipid levels and liver enzymes in the normal range before treatment should be monitored in the second month of the treatment, and if the values are normal, no further analysis is required [4]. In the current study, serum lipid and liver enzyme levels were found to be statistically significantly higher during the treatment than pre-treatment, but this situation did not require discontinuation of treatment.

When haematological parameters were evaluated, the PCT, PLT, RDW, MCV, HCT, HGB and LYM parameters were determined to be statistically significantly higher during treatment compared to the pre-treatment levels, while the NEU parameter was lower. When PLT, PCT and LYM parameters were evaluated in respect of gender, these parameters were significantly more varied in females than in males.

All Trans Retinoic Acid (ATRA) is a derivative of vitamin A. Since it allows the growth, differentiation and apoptosis of myeloid stem cells via CD34+ in bone marrow cells, it is used in the treatment of myelodysplastic syndrome [10]. Previous studies have demonstrated that ATRA increased the neutrophil and platelet counts and hemoglobin concentration [11]. Seçkin et al. (2016) also reported that they found HGB and PLT parameters to be statistically significantly higher considering the fact that isotretinoin is also a vitamin A derivative, which can increase bone marrow with similar effects [12].

In this study, the HGB, HCT and PLT parameters during treatment were found to be higher than pre-treatment. However, the NEU parameter was found to be lower than the pre-treatment value. A significant increase in the PLT parameter was also detected in the study conducted by Karadag et al. (2013), while no difference was found in the HGB, HCT and WBC parameters [13]. In another study, no significant difference in HGB, HCT and WBC parameters was found, whereas the PLT parameter was found to be significantly lower [14].

It is known that isotretinoin reduces TNF, IL-4, IL-17 and IFN-γ levels and is an anti-inflammatory and immunoregulatory drug [15]. In the current study, the effect of isotretinoin on inflammation was evaluated by examining inflammatory parameters (NLR, PLR, WBC, RDW and NEU). NLR and PLR are commonly used inflammatory markers that can be calculated from hematological parameters. NLR and PLR markers can be used to assess systemic inflammation in patients with psoriasis [16]. While there was no significant difference in NLR, PLR and WBC parameters in the current study, the RDW value increased and the NEU parameter decreased significantly. Seçkin et al. (2016) found that the WBC, NLR and PLR parameters did not change, while the RDW parameter was low [12]. In another study, it was revealed that PLT, PCT, WBC, NEU and MCV parameters differed during treatment and these changes appeared to fluctuate every month, but no significant difference was detected in other hematological parameters [17].

In the light of these findings, it can be said that a distinguishing feature of this study was that biochemical values and hematological parameters were extensively evaluated using more comprehensive data. Group comparisons were made according to gender and age variables, which have not been included in previous studies. In addition, the Repeated Measures ANOVA test was used in the statistical analysis.

Conclusion

Although some serum lipid and hepatic enzyme levels in this study varied during isotretinoin treatment, they generally remained within the normal range and did not lead to a condition that would require discontinuation of treatment. Hematological parameters varied in the same way. Some of the inflammatory parameters varied significantly (RDW ↑, NEU ↓), some did not change (WBC, NLR and PLR), and HGB, HCT and PLT parameters were found to be high. However, since the mean ± standard deviation values remained within normal limits, there was no need to discontinue treatment and no effect on the patient was seen. In light of all these findings, it can be said that oral isotretinoin treatment has a limited effect on hematological parameters, serum lipid levels, liver enzymes and renal functions. Therefore, it is recommended that patients should be checked for laboratory tests less frequently if there is no hepatic or haematologic disease prior to treatment. It is recommended that hematological parameters be monitored before treatment and not monitored during treatment unless an abnormal condition is present. This can be regarded as an important implication in terms of providing cost-effective healthcare services and preventing patients from undergoing unnecessary invasive procedures.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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