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A RETROSPECTIVE ANALYSIS OF ABNORMAL LABORATORY FINDINGS IN SUBJECTS TREATED WITH ORAL ISOTRETINOIN

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Abstract

Background: Isotretinoin is used for the treatment of moderate to severe acne that can raise cholesterol, triglycerides, and liver enzyme levels necessitating laboratory monitoring. However, monitoring frequency varies.

Aim: To assess the frequency of laboratory abnormalities concerning liver aminotransferases, cholesterol, and triglycerides in acne subjects treated with isotretinoin to evaluate the frequency of laboratory monitoring in subjects with isotretinoin to assess the association between laboratory abnormalities and body weight.

Methods: The present retrospective study included 204 subjects treated with oral isotretinoin for acne vulgaris for a minimum of 4 months and were assessed for laboratory parameters including liver aminotransferases, cholesterol, and triglycerides at baseline and last visit. The data gathered were analyzed statistically using SPSS software and results were formed.

Results: After oral isotretinoin**,** liver enzyme levels for AST and ALT showed non-significant changes in normal and high values at baseline, follow-up, and last visits with p=0.33 and 0.42 respectively for AST and ALT values. For levels of TC and TG, a significant increase was seen at the follow-up dose with p<0.000. Higher body weight subjects had significantly higher levels of TG, AST, and ALT compared to normal weight subjects with p<0.05. The cumulative dose of oral isotretinoin had a non-significant association with TG, TC, ALT, and AST.

Conclusion: Oral isotretinoin can elevate the levels of triglycerides, total cholesterol, AST, and ALT. However, the incidence of these elevations is low and not associated with any morbidity with no stronger evidence suggesting reconsideration of the monthly laboratory monitoring of these parameters. Subjects with high weight are at risk and need more frequent monitoring.

Keywords: acne vulgaris, cholesterol, isotretinoin, liver enzymes, triglycerides

INTRODUCTION

Acne is one of the most common conditions affecting the skin and is a follicular disease. Acne has two stages including the inflammatory stage and the comedonal stage. In the comedonal stage, a comedon formation occurs following the faulty keratinization leading to a hyperkeratotic plug that blocks the pilosebaceous cell opening.[1] Excess sebum production known as seborrhea causes the dilatation of the follicle contributing to the overgrowth of bacteria known as Propionibacterium acne which is a follicular colonizer causing a follicular rupture and leukocyte infiltration. These follicular contents trigger the inflammation and bacterial metabolites leading to the formation of pustules and papules.[2] Acne formation is also contributed by DHEAS (dehydroepiandrosterone sulfate). Post-inflammatory hyperpigmentation and scarring are typical residual skin changes seen after acne which affects nearly 79% to 95% of teenagers. The youth population is predominantly affected by acne, but can also affect adults and children.[3]

Owing to the compromise of esthetics by acne, it negatively affects the psychology of the affected subjects, especially the females along with the impact on the quality of life. Subjects having acne are more likely to have psychological disorders including depression and anxiety. The treatment of acne can help subside these symptoms.[4]

Treatment of acne is governed by disease severity. In subjects having mild-inflammatory or non-inflammatory acne, topical antibiotics, azelaic acid, benzoyl peroxide, adapalene, and/ or topical tretinoin are either used alone or in combination. Treatment of severe or moderate inflammatory acne is done with isotretinoin. Isotretinoin is also used to treat acne which is resistant to other treatments including topical agents and antibiotics.[5]

The dose of isotretinoin used for the treatment of acne vulgaris ranges from 0.5mg/kg to 2mg/kg per day given orally for 16-24 weeks. The cumulative dose usually recommended for isotretinoin for treating acne is 120-150 mg/kg. Isotretinoin is a drug derived from vitamin-A has a powerful anti-sebum effect reducing the size and activity of the sebaceous gland which normalizes the keratinization of the sebaceous follicle and reduces the number of Propionibacterium acnes.[6]

Various side-effects are being associated with the use of oral isotretinoin including various laboratory changes like the elevation of total cholesterol, TG (triglycerides), and liver enzymes. The most serious reported side-effect is teratogenicity and the most common mucocutaneous side-effect is dryness of nasal mucosa, skin, and dry cracked lips.[7]

In various studies conducted in the literature, the incidence of laboratory abnormalities in subjects treated with isotretinoin is reported to have wide variability by various scholars and physicians. The routine practice of monthly monitoring of the laboratory parameters in subjects with oral isotretinoin treatment has limited and lacks evidence. Hence, the present study was done to assess the frequency of laboratory abnormalities concerning liver aminotransferases, cholesterol, and triglycerides in acne subjects treated with isotretinoin to evaluate the frequency

of laboratory monitoring in subjects with isotretinoin to assess the association between laboratory abnormalities and body weight.

MATERIALS AND METHODS

The present retrospective clinical study was done to assess the frequency of laboratory abnormalities concerning liver aminotransferases, cholesterol, and triglycerides in acne subjects treated with isotretinoin to evaluate the frequency of laboratory monitoring in subjects with isotretinoin to assess the association between laboratory abnormalities and body weight. The study was done at Department of Dermatology, Sri Balaji Institute of Medical Sciences, Raipur. The study population was comprised of subjects from the Department of Dermatology of the Institute.

The study included the subjects who were on oral isotretinoin for the management of acne vulgaris in the defined study period and had undergone at least two laboratory tests during the treatment with isotretinoin including TC (total cholesterol), TG (triglycerides), ALT (alanine aminotransferase), and AST (aspartate aminotransferase).

After final inclusion, detailed history was recorded for all the subjects along with the clinical examination. Data were obtained from the medical records of the subjects including lab investigations, baseline laboratory parameters, follow-up laboratory parameters, starting dose, dose at the treatment end, treatment duration, gender, and age of the subjects.

SPSS software was used to perform the statistical analysis along with the review of laboratory results of the subjects and laboratory parameters were compared from the baseline to the follow-up laboratory parameters recorded at the end of the treatment. The study also assessed the relationship between laboratory abnormalities and the total cumulative dose of oral isotretinoin. The study also assessed the relationship between laboratory changes and body weight during the treatment course.

A total of 1152 subjects with acne vulgaris treatment were screened for the study. 749 subjects were excluded as they were not treated with oral isotretinoin. A total of 429 subjects received oral isotretinoin for the treatment of their acne. Among these 429 subjects, 225 subjects did not meet the inclusion criteria and were excluded from the study. The final sample size was constituted of 204 study subjects that met the inclusion criteria.

In these 204 study subjects, the changes in TC, TG, ALT, and AST were assessed. The analysis of TC, TG, ALT, and AST was done based on the NCEP (national cholesterol education program) guidelines. The levels of AST and ALT were classified as normal with <40 U/L and high as ≥40 U/L. Total cholesterol levels were classified as normal at 200mg/dl and high as >200mg/dl, and triglyceride levels were classified as normal at ≤150 mg/dL and high as ≤150 mg/dL.

The data collected were assessed statistically using logistic regression and multivariate statistical techniques. The data were presented in tabulated and descriptive formats. SPSS version 22.0, 2013, Armonk, NY: IBM Corp and chi-square and t-test were utilized. The data were expressed as mean and standard deviations and as percentages and numbers with a 0.05% significance level.

RESULTS

The present retrospective clinical study was done to assess the frequency of laboratory abnormalities concerning liver aminotransferases, cholesterol, and triglycerides in acne subjects treated with isotretinoin to evaluate the frequency of laboratory monitoring in subjects with isotretinoin to assess the association between laboratory abnormalities and body weight. The study included 204 subjects from both genders managed with oral isotretinoin for acne vulgaris. The mean age of the study subjects was 22.17±0.4 years. There were 50.98% (n=104) males and 49.01% (n=100) females in the present study. The starting mean dose of oral isotretinoin in the study subjects was 34.22±0.7 mg which at the end was 37.46±0.6 mg. The cumulative dose was 6741.96±253.9 mg in the study subjects**.** The mean body weight of the study subjects was 66.7±0.7 kg as shown in Table 1.

On assessing the laboratory parameters in the study subjects at a different time intervals, the results are summarized in Table 2. Triglyceride levels were normal in 186 subjects at baseline compared to high levels in 13 subjects which at follow-up visits were seen raised high levels in 18 subjects and normal levels were seen in 92 subjects, and at the last visit, normal levels in higher (n=172) subjects and high levels in lesser (n=25) subjects. This difference was statistically significant with p<0.000. Total cholesterol levels at baseline were normal in a higher number of subjects (n=178) which decreased to 97 subjects at follow-up and again seen in higher subjects at the last visit in 171 subjects. High levels of TC were seen in 21 subjects at baseline, 12 subjects at follow-up, and 17 subjects at the last visit. These changes in total cholesterol levels were also statistically significant with p<0.000. The liver enzyme levels for AST and ALT showed non-significant changes in normal and high values at baseline, follow-up, and last visits with p=0.33 and 0.42 respectively for AST and ALT values (Table 2).

Concerning the correlation of body weight and laboratory parameters in study subjects at different time intervals, it was seen that for body weight and TG levels at baseline, in subjects with normal TG levels mean body weight was 65.6±16.3 and was higher for high levels of TG with 81.2±19.5 kg. The body weight in subjects with normal TG at the last visit was significantly lesser, 64.6±16.3 compared to subjects with higher TG where the body weight was 77.7±16.3 with p=<0.000. In subjects with normal TC, the body weight at the last visit was comparable to subjects with high TC with respective values of 66.5±17.2 and 66.3±15.2 with p=0.92. For subjects with normal ALT levels at the last visit, body weight was significantly lesser than the weight of subjects with high ALT levels with p=0.05. For subjects with normal AST levels at the

last visit, the body weight was 66.4±16.7kg which was significantly lower compared to subjects with high AST levels, where the body weight was 75.6±22.5 with p=0.05 as depicted in Table 3.

For the cumulative dose of oral isotretinoin at the last visit in the study subjects, it was seen that for triglycerides, independent t-test, df, and p-values were 0.744, 387, and 0.454 respectively showing non-significant relation between cumulative dose and triglyceride levels. For total cholesterol respective independent t-test, df and p-values were 0.835, 382, and 0.407 again showing a non-significant association between total cholesterol levels and cumulative dose of oral isotretinoin at the last visit. A similar non-significant association was seen for ALT and AST levels with the cumulative dose of oral isotretinoin at the last visit with respective p-values of 0.812 and 0.234 respectively as summarized in Table 4.

DISCUSSION

The present study included 204 subjects from both genders managed with oral isotretinoin for acne vulgaris. The mean age of the study subjects was 22.17±0.4 years. There were 50.98% (n=104) males and 49.01% (n=100) females in the present study. The starting mean dose of oral isotretinoin in the study subjects was 34.22±0.7 mg which at the end was 37.46±0.6 mg. The cumulative dose was 6741.96±253.9 mg in the study subjects**.** The mean body weight of the study subjects was 66.7±0.7 kg. These data were compared to the studies of Cordain L et al[8] in 2002 and Plewig G et al[9] in 2007 where authors assessed subjects with demographics comparable to the present study in their respective studies.

The study results showed that for the laboratory parameters in the study subjects at a different time intervals, the results are summarized in Table 2. Triglyceride levels were normal in 186 subjects at baseline compared to high levels in 13 subjects which at follow-up visits were seen raised high levels in 18 subjects and normal levels were seen in 92 subjects, and at the last visit, normal levels in higher (n=172) subjects and high levels in lesser (n=25) subjects. This difference was statistically significant with p<0.000. Total cholesterol levels at baseline were normal in a higher number of subjects (n=178) which decreased to 97 subjects at follow-up and again seen in higher subjects at the last visit in 171 subjects. High levels of TC were seen in 21 subjects at baseline, 12 subjects at follow-up, and 17 subjects at the last visit. These changes in total cholesterol levels were also statistically significant with p<0.000. The liver enzyme levels for AST and ALT showed non-significant changes in normal and high values at baseline, follow-up, and last visits with p=0.33 and 0.42 respectively for AST and ALT values. These results were consistent with the studies of Kizilyel O et al[10] in 2014 and Lee YH et al[11] in 2016 where authors reported similar changes in laboratory parameters after oral isotretinoin for acne vulgaris as shown in the present study.

For the assessment of the correlation of body weight and laboratory parameters in study subjects at different time intervals, it was seen that for body weight and TG levels at baseline, in subjects with normal TG levels mean body weight was 65.6±16.3 and was higher for high levels of TG with 81.2±19.5 kg. The body weight in subjects with normal TG at the last visit was significantly

lesser, 64.6±16.3 compared to subjects with higher TG where the body weight was 77.7±16.3 with p=<0.000. In subjects with normal TC, the body weight at the last visit was comparable to subjects with high TC with respective values of 66.5±17.2 and 66.3±15.2 with p=0.92. For subjects with normal ALT levels at the last visit, body weight was significantly lesser than the weight of subjects with high ALT levels with p=0.05. For subjects with normal AST levels at the last visit, the body weight was 66.4±16.7kg which was significantly lower compared to subjects with high AST levels, where the body weight was 75.6±22.5 with p=0.05. These results were in agreement with the findings of Sharma P et al[12] in 2021 and Hansen TJ et al[13] in 2016 where authors reported a similar association between high body weight and triglyceride and cholesterol levels as in the present study.

Concerning the cumulative dose of oral isotretinoin at the last visit in the study subjects, it was seen that for triglycerides, independent t-test, df, and p-values were 0.744, 387, and 0.454 respectively showing non-significant relation between cumulative dose and triglyceride levels. For total cholesterol respective independent t-test, df and p-values were 0.835, 382, and 0.407 again showing a non-significant association between total cholesterol levels and cumulative dose of oral isotretinoin at the last visit. A similar non-significant association was seen for ALT and AST levels with the cumulative dose of oral isotretinoin at the last visit with respective p-values of 0.812 and 0.234 respectively. These results were in line with the studies of Oktem A et al[14] in 2019 and Barbieri JS et al[15] in 2020 where authors also reported a non-significant association between body weight and cumulative dose of oral isotretinoin in subjects of their respective studies as in the present study.

CONCLUSION

Considering its limitations, the present study concludes that Oral isotretinoin can elevate the levels of triglycerides, total cholesterol, AST, and ALT. However, the incidence of these elevations is low and not associated with any morbidity with no stronger evidence suggesting reconsideration of the monthly laboratory monitoring of these parameters. Subjects with high weight are at risk and need more frequent monitoring. In subjects with no increase in the dose of oral isotretinoin, frequent laboratory monitoring poses a high emotional and financial burden. The limitations of this study were smaller considered population, shirt monitoring, and biased related to the geographic location warranting further long-term studies planned longitudinally.

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TABLE

Characteristics	**Mean ± S. D**
Mean age (years)	22.17±0.4
Gender n (%)	
Males	104 (50.98)
Females	100 (49.01)
Starting dose (mg)	34.22±0.7
Dose at the end (mg)	37.46±0.6

Cumulative dose (mg)	6741.96±253.9
Body weight (kg)	66.7±0.7

Table 1: Demographic data of the study subjects

Laboratory parameter	**Baseline n (%)**	**Follow-up n (%)**	**Last visit n (%)**	**p-value**
TG normal vs high	186 vs 13	92 vs 18	172 vs 25	**<0.000**
TC normal vs high	178 vs 21	97 vs12	171 vs 27	**<0.000**
ALT normal vs high	171 vs 24	97 vs 12	171 vs 17	0.42
AST normal vs high	184 vs10	104 vs 6	188 vs 7	0.33

Table 2: Assessment of laboratory parameters in study subjects at the different time intervals

Parameters vs body weight	**Normal level (Mean ± S. D)**	**High level (Mean ± S. D)**	**p-value**
Body weight and TG (baseline)	65.6±16.3	81.2±19.5	
Body weight and TG (last visit)	64.6±16.3	77.7±16.3	**0.000**
Body weight and TC (baseline)	66.3±16.7	70.7±17.5	
Body weight and TC (last visit)	66.5±17.2	66.3±15.2	0.92
Body weight and ALT (baseline)	65.3±16.4	76.3±18.2	
Body weight and ALT (last visit)	66.3±16.7	76.4±18.4	**0.001**
Body weight and AST (baseline)	66.3±16.4	77.5±22.2	
Body weight and AST (last visit)	66.4±16.7	75.6±22.5	**0.05**

Table 3: Correlation of body weight and laboratory parameters in study subjects at different time intervals

Cumulative dose at last visit levels	**Independent t-test**	**df**	**p-value**
TG	0.744	387	0.454
TC	0.835	382	0.407
ALT	-0.242	372	0.812
AST	1.194	374	0.234

Table 4: Relationship between cumulative dose and laboratory parameters in the study subjects