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Original Article

Dermatology Section

Effect of Isotretinoin on Thyroid Function Test in Acne Patients

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ABSTRACT

Introduction: With the rising popularity of Isotretinoin for acne vulgaris treatment, the interest in knowing the effect of oral Isotretinoin on endocrine function and the metabolic processes has increased considerably.

Aim: To study the effect of Isotretinoin on serum thyroid hormone levels in acne patients and to study side effects of Isotretinoin, if any.

Materials and Methods: In this interventional from September 2018-August 2019, using purposive method, 30 patients (Twenty males and Ten females) between age group 15-30 years-old having grade 3 (20 patients) and 4 (10 patients) acne vulgaris (according to standard system of grading) were enrolled and were started on oral capsule Isotretinoin 0.5 mg/kg/day for at least three months. A baseline thyroid profile which includes serum Triiodothyronine (T3), serum Thyroxine (T4) and Thyroid Stimulating Hormone (TSH) was performed on all subjects before and after three months of continued treatment. p-value <0.05 was considered as significant.

Results: After three months of continuous oral Isotretinoin administration, it was observed that serum T3 and T4 values were raised while serum TSH was slightly reduced as compared to baseline values but the difference was not statistically significant. It was also observed that lip cheilitis was the most common side effect manifesting in 28 out of 30 patients.

Conclusion: In the study, minor alteration in thyroid profile was observed but the difference was statistically not significant. Thus, it can be concluded that Isotretinoin can be safely given upto three months without any disturbance in thyroid function tests.

Keywords: Acne vulgaris, Adverse effects, Hormone imbalance, Monitoring, Retinoids

INTRODUCTION

The United States Food and Drugs Administration (USFDA) in 1982 approved Isotretinoin for the management of severe forms of acne vulgaris [1]. An active metabolite of vitamin A, it has been the drug of choice for moderate to severe acne vulgaris, disorders of keratinization and sebaceous gland as well as prevention of skin cancers [2].

Till date, the efficacy of Isotretinoin has remained unbeatable. Even decades later, Isotretinoin still remains the best available clinically effective treatment for acne vulgaris compared to other acne treatment options. With the rising popularity of Isotretinoin, especially for the treatment of acne vulgaris, the interest has considerably increased in knowing the effect of this retinoid on endocrine function and the metabolic processes [2].

The thyroid hormones are both directly and indirectly involved in lipid metabolism of the human body. A 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) reductase which mediates the first and foremost step in cholesterol biosynthesis is induced by thyroid hormones. Considering the thyroid hormone-serum lipid interaction, studies suggesting altered serum lipid profile following retinoid use, paved way for exploration of possible effect on thyroid function if any [3].

Various studies have suggested that Isotretinoin causes thyroid dysfunction but a thorough literature search regarding the effects on serum thyroid hormone levels following the use of oral Isotretinoin in acne vulgaris patients revealed conflicting results [2-8].

Following use of Isotretinoin, the effect on serum thyroid hormone levels, if any has to be observed in the acne patients receiving the drug for more than three months as the health of young population who constitute the bulk of the population suffering from acne is at stake. Using the drug in patients having pre-existing thyroid dysfunction or having clinically proven hypo or hyperthyroidism may cause further worsening of their condition. Hence, this study was undertaken with the aim of studying the effect of Isotretinoin on thyroid function tests in acne patients while assessing its side effects, if any.

MATERIALS AND METHODS

This Quasi experimental study was conducted at a tertiary care hospital from September 2018-August 2019. Institutional Ethics Committee approval was obtained before commencement of the study (Ref.No. DMIMS (DU)/IEC/2018-19/7486) and a valid informed consent was taken from each study participant. Being a purposive study, the sample size were 30 patients of both genders between age group of 15-30 years old suffering from grade 3 and grade 4 acne vulgaris attending dermatology Outpatient Department (OPD). Sample size was estimated to be 30 using Open Epi software to detect a mean difference of 5 between pre and post-intervention values with 95% Confidence level, 90% power and assuming a 5% attrition.

A detailed history regarding age, sex, educational status, marital status, duration of acne vulgaris, personal history, family history, and treatment history was taken.

Inclusion criteria: Patients of both genders and age group 15-30 years old, having grade 3 and grade 4 acne vulgaris and patients who were willing to give consent for participating in the present study were included in the study.

Exclusion criteria: Patients suffering from any major systemic disease/s, uncontrolled medical or surgical illness, those who were a known case of hypothyroidism, hyperthyroidism, hypopituitarism or hyperpituitarism, pregnant or lactating or unconsenting patients were excluded from the study.

A detailed clinical examination of patients of acne vulgaris was done and assessment of acne vulgaris severity was done by using a standard system of grading [Table/Fig-1] [9].

Grading	Clinical features
Grade 1	Comedones, occasional papules
Grade 2	Papules, comedones, few pustules
Grade 3	Predominant pustules, nodules, abscesses
Grade 4	Mainly cysts, abscesses, widespread scarring

[Table/Fig-1]: Grading of acne vulgaris [9].

All the enrolled patients were prescribed oral capsule Isotretinoin at 0.5 mg/kg/day at night time after a fatty meal.

A baseline serum thyroid function test which included serum T3, T4 and TSH was carried out by taking venous blood samples from the subjects after 8 hours of overnight fasting before starting the drug and the patients were asked to follow-up after 3 months of continued oral Isotretinoin therapy with repeat thyroid profile and for assessment of common side effects like lip cheilitis for which Isotretinoin Cheilitis Grading Scale (ICGS) was used [10].

STATISTICAL ANALYSIS

Categorical variables in the results were presented in the form of number as well as percentage (%) while continuous variables were presented in the form of mean±SD and median. The analysis of statistics was performed using inferential and descriptive statistical methods while student's paired t-test was used to assess the comparison between baseline thyroid profile values with that of three months after continued Isotretinoin administration. Software used in the analysis was Statistical Package for Social Sciences (SPSS) version 24.0 and level of significance was considered as $p<0.05$.

RESULTS

Twenty males and ten females (Total 30 of patients) were included in this study. Mean age of the cohort was 19.3±3.14 years (age range of 15-30 years). In this study, patients suffering from grade 3 (20 patients) and grade 4 (10 patients), also considered as severe forms of acne vulgaris were observed. Out of grade 4 acne patients, 8 were males and 2 were females. On the other hand, out of grade 3 patients, 12 were males and 8 were females.

In the present study, out of 30 patients 28 subjects (93.33%) experienced lip cheilitis while only 2 patients reported no such complaint. The onset of cheilitis was noted within three weeks of treatment and continued throughout the treatment period. The patients were adequately counselled about lip dryness prior to initiation of Isotretinoin. Skin dryness was reported by 11 (36.67%) patients after starting Isotretinoin. Patients were prescribed lip balms and moisturisers for above complaints.

Baselines mean value of serum T3 was 1.15 and after 3 months of Isotretinoin administration was 1.28. The mean difference was 0.12±0.40. Therefore, although the serum T3 values were raised as compared to baseline values, the difference was not significant (p-value- 0.095).

Baselines mean value of serum T4 was 7.4 and after 3 months of Isotretinoin administration was 7.73. The mean difference was 0.33±2.13 while p-value was 0.40 which was statistically not significant [Table/Fig-2].

DISCUSSION

Out of all the previous studies quoted, the one conducted by O Leary TJ et al., is in accordance to the present study where even after 12 weeks of continued Isotretinoin administration, they observed no change in thyroid function test. Similarly, in a study conducted by AL Saif et al., no significant change was observed in serum TSH levels while the free T4, thyroid anti peroxidase (Anti TPO) and Thyroglobulin levels remained unchanged despite 8 months of isotretinoin therapy in acne patients. Also, in majority of the studies it was observed that higher dose of Isotretinoin was administered as compared to the present study [Table/Fig-3] [2,5-8,11].

In the present study, out of 30 patients, 28 patients (93.33%) complained of lip cheilitis while 11 patients (36.67%) complained of skin dryness over face during their monthly follow-up visits. Known side effects of retinoids like altered differentiation and shedding of epidermis contributes to poor barrier function and photosensitivity which may lead to manifestations like lip cheilitis and skin dryness [12]. In the present study, the treatment duration was of three months as suggested in the study by Rao PK et al., where they inferred that three months of Isotretinoin administration is advisable for effective management of moderate to severe forms of acne which is in concordance to the present study [13].

Retinoids exert their effects on target cells by binding and activating nuclear retinoid receptors as Retinoic Acid Receptors (RARs) and Retinoid X Receptors (RXRs), which are members of steroid-thyroid hormone super family [14,15]. RXR selective retinoids are known to influence vitamin D and thyroid hormone responsive genes.

Parameter		Mean	N	Standard deviation	Standard error mean	Mean difference	Stats
T3	Baseline value	1.15	30	0.21	0.03	0.12±0.40	t-value=1.77 p-value=0.095,
	After three months of Isotretinoin	1.28	30	0.37	0.06		
T4	Baseline value	7.40	30	1.51	0.27	0.33±2.13	t-value=0.85 p-value=0.40,
	After three months of Isotretinoin	7.73	30	1.81	0.33		
TSH	Baseline value	2.53	30	1.14	0.20	0.01±1.44	t-value=0.03 p-value=0.96,NS
	After three months of Isotretinoin	2.52	30	1.46	0.26		

[Table/Fig-2]: Comparison of baseline serum T3, T4 and TSH levels and post three months of Isotretinoin administration.
Student's paired t-test was used; p-value<0.05 to be considered significant; T3: Triiodothyronine; T4: Thyroxine; TSH: Thyroid stimulating hormone

Authors	Sample size	Dose/Duration of Isotretinoin	Increased	Decreased	No change
O'Leary TJ et al., [6]	24 female acne patients	1 mg/kg/day for 12 weeks (for TSH 8 weeks)			FreeT3, FreeT4 and TSH
AL Saif F et al., [8]	51 acne patients	0.5 mg/kg/day			FreeT4,TSH,TPO,TGA
Marsden JR et al., [5]	7 rosacea patients	1 mg/kg/day for 12 weeks		T3,T4,free thyroxine index	TSH
Uyar B et al., [2]	66 acne patients	0.5-0.8 mg/kg/day for 16 weeks	TSH	FT3,FT4, anti-TPO, thyroid volume	Anti-Tg
Karadag AS et al., [7]	47 acne patients	0.5-0.75 mg/kg/day for 12 weeks		FT3,TSH, TRAb	Thyroglobulin, anti-Tg,anti-TPO, FT4
Silva ACM et al., [11]	Adult female rats	Isotretinoin for 28 days	Serum T3		Serum T4,TSH
Present study	30 acne patients	0.5 mg/kg/day for 3 months			No significant change in serum T3,T4,TSH

[Table/Fig-3]: Findings of previous clinical trials and present study regarding the effects of Isotretinoin on thyroid gland parameters [2,5-8,11].
TRAb: TSH receptor antibodies; fT3: Free triiodothyronine; fT4: Free thyroxine; TSH: Thyroid stimulating hormone; TPO: Thyroid peroxidase; Anti-Tg: Anti-thyroglobulin

All the retinoids have affinity for atleast one (α, β, ϒ) or many receptors of the RAR or RXR or both families except Isotretinoin which does not bind to any receptor RAR or RXR. This may be the key mechanism which explains the lack of effect of Isotretinoin on thyroid function as observed in present study. It has been postulated by a study that isotretinoin may act as a pro-drug that is converted intracellularly to metabolites that are agonists for RAR and RXR nuclear receptors, this phenomenon has been poorly understood till date [16]. On the other hand, Bexarotene is selective for RXR receptor and is clinically used in the treatment of cutaneous T cell lymphoma. Bexarotene is associated with severe central hypothyroidism with high frequency, associated with marked reductions in concentrations of TSH and thyroxine [17].

Limitation(s)

Small sample size and short follow-up period were important limitations. Since the dosage and duration of Isotretinoin administered in the present study subjects was fixed at 0.5 mg/kg/day and three months, respectively, the effect of Isotretinoin at variable doses and time duration was not evaluated. Also, in the present study, total serum T3, total serum T4 and TSH were evaluated. While serum free T3 and free T4 which indicate more accurate serum hormone levels were not evaluated.

CONCLUSION(S)

In the study, minor alterations in the levels of T3, T4 and serum TSH were observed but the difference was statistically not significant. Thus, it can be concluded that there was no significant effect observed on thyroid function test and Isotretinoin can be safely given upto three months. It is recommended that further studies need to be conducted to assess the effect of continued oral Isotretinoin on serum thyroid hormone levels in acne vulgaris patients at variable doses and for variable time duration. Moreover, action of other metabolites of Isotretinoin on nuclear receptors also needs further exploration.

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