ISSN: 2091-2749 (Print)
2091-2749 (Print)

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Association of dry eye syndrome with oral Isotretinoin therapy for severe nodulocystic acne and recalcitrant acne vulgaris

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ABSTRACT

Introductions: Oral Isotretinoin was registered in Nepal almost three decades later its first introduction in the USA. It remains the most clinically effective medication for acne. Dry eye syndrome is a 'certain' adverse effect of oral Isotretinoin therapy which can be validated by tear film break up time and Schirmer I tests.

Methods: Fifty patients aged above 12 years presenting to Dermatology outpatient department of Dhulikhel Hospital with severe nodulocystic acne or recalcitrant acne vulgaris not responding to three months of systemic antibiotics along with topical agents were included. Tear film break up time and Schirmer I tests before, at 45 and 90 days, and one month after taking oral Isotretinoin were performed to study association of dry eye syndrome due to oral Isotretinoin.

Results: Both eyes of fifty selected patients were sampled. Baseline mean tear film break up time of 12.37±4.17sec decreased to 9.69±3.70sec, 9.09±3.77sec and 10.67±3.50sec at 45 and 90 days and on follow up, respectively. Likewise, baseline mean Schirmer I value of 16.68 ± 8.73mm decreased to 12.26 ±7.64mm, 11.49 ± 8.07mm and 11.76 ± 8.11mm respectively at 45 and 90 days and on follow up. The differences between the mean values were analyzed using paired samples T test and all were statistically significant except between the mean Schirmer values at 90 days and on follow up.

Conclusions: Abnormal mean tear break up time at 45 and 90 days in this study suggests that dry eye syndrome was caused by oral Isotretinoin during acne therapy but tends to revert to normal on cessation.

Keywords: acne vulgaris, dry eye syndromes, isotretinoin, severe nodulocystic acne

INTRODUCTION

Oral Isotretinoin (13-*cis*-retinoic acid), was first approved in 1982 by the United States Food and Drug Administration (FDA) for the treatment of severe recalcitrant nodulocystic acne that is unresponsive to conventional therapy including systemic antibiotics.[1,2] Even after three decades, it remains the most clinically effective medication for acne.[3]

Abnormal Meibomian gland secretion leading to ocular sicca (dry eye) is a 'certain' side effect of oral Isotretinoin therapy.[4] Dry eye syndrome (DES) is a clinical condition characterized by deficiency of tear production or instability of tear film leading to excessive tear evaporation resulting in ocular discomfort and visual disturbance as well as potential damage to the ocular surface.[5] Schirmer test and tear film break-up time (BUT) are used to grade DES.[6]

Research regarding Oral Isotretinoin which is relatively new to Nepal, is lacking.[7] This study elucidate the extent of eye dryness caused by oral Isotretinoin therapy.

METHODS

It was a cross sectional study conducted in the Dermatology outpatient department (OPD) of Dhulikhel Hospital from April 2013 to April 2014. The Institutional Review Committee of Kathmandu university School of Medical Sciences, Dhulikhel Hospital (IRC-KUSMS) approved the study in 15 March 2013. Verbal and written consent were taken from all the patients (or a parent incase of minor) selected for the study after careful counseling.

Patients seeking medication for acne, who presented to Dermatology OPD of Dhulikhel Hospital, from April 2013 till December 2013, were evaluated and those with severe nodulocystic acne or recalcitrant acne vulgaris (acne not responding to three months of systemic antibiotics along with topical agents) were chosen.[2,8] Among them, only patients more than 12 years of age (European Directive on Isotretinoin Prescribing) were selected.[2] Thorough medical history- taking, clinical examination and baseline blood investigations including complete blood count, erythrocyte sedimentation rate, liver function tests, renal function tests, random blood sugar and fasting lipid profile were done.

In case of females, with additional informed consent, urine examination to detect pregnancy was also done and was repeated on subsequent visits during the study. Female patients found to be pregnant or those who were planning to become pregnant within four months of the study period were strictly excluded from the study as Isotretinoin is a Category X drug.[9] Oral or systemic hormonal contraception were not allowed, to avoid interaction with Isotretinoin.[1] Physical methods of contraception were encouraged. Guidelines for pregnancy monitoring as per the textbook[2] was not followed due to Nepalese social stigma of contraception in the unmarried.

Patients currently or two weeks prior to initiating the study, taking systemic or ocular medication were excluded from the study. Patients who are or had in the past taken oral Isotretinoin were also excluded. Patients found to have ocular disease and co-morbid conditions like: atopic dermatitis, bronchial asthma, hypertention, diabetes, hyperlipidemia, anemia, bleeding disorders, hemorrhoids, anal fissures, tuberculosis and keloids were excluded from the study.
All consenting patients fulfilling the above criteria were prescribed fixed regimen of Oral soft gel capsules of Isotretinoin (0.3 mg/kg daily) after dinner for 90 days; oral tablet Prednisolone (0.2 mg/kg daily; to avoid initial acne flare due to Isotretinoin) after lunch and oral tablet Pantoprazole (0.7 mg/kg daily; to prevent acid peptic disease from Prednisolone) on empty stomach for initial 10days; and Petroleum Jelly application for chapped lips and dry skin.

Besides examination in the Dermatology OPD, the patients were required to undergo eye check-up along with BUT and anesthetized Schirmer's test (Schirmer I) in the Ophthalmology OPD by a single ophthalmologist prior to starting the therapy (baseline); 45 and 90 days of therapy and; 30 days after completion of therapy (follow up).

Those patients who developed allergic reaction or intolerance to the therapy and; patients requiring additional systemic or ocular medication during the study were further excluded from the study. Initially consenting patients who during the study period wanted to withdraw and; non-compliant patients who did not turn up for follow-up examination on the specified date were excluded as well.

In the Ophthalmology OPD, BUT was done prior to Schirmer I, the procedure of which are enlisted below.[5,10]

BUT:

The test was performed as follows,

a. Fluorescein 2% was instilled into the lower fornix of the right eye.
b. The patient was asked to blink several times.
c. The tear film was examined with a broad beam and a cobalt blue filter.
d. After an interval of time, black spots or lines appeared in the fluorescein stained film.
e. The interval between the last blink and the appearance of the first randomly distributed dry spot was the BUT and was noted.
f. The above procedure was repeated for the left eye.

Schirmer I:

The test was performed as follows,

a. A drop of 2% Lignocaine solution was instilled into the lower fornix of the right and left eye.
b. Excess tears and instillation were gently removed from the fornix with a tissue paper.
c. 5×35 mm strip of Whatman filter papers were folded 5mm from one end and inserted at the junction of the middle and outer third of the lower lids, without touching the cornea or lashes.
d. The patient was asked to keep the eyes gently closed.
e. After 5 minutes, the Whatman papers were removed and the amounts of wetting from the fold were measured in mm and noted.

The DES is a clinical condition characterized by deficiency of tear production or instability of tear film leading to excessive tear evaporation resulting in ocular discomfort and visual disturbance as well as potential damage to the ocular surface.[5] Ocular surface dye staining, BUT, Schirmer test, fluorescein clearance test, lacrimal gland function and tear osmolarity are clinical tests available for the diagnosis of dry eye. However, no single test is adequate for establishing the diagnosis. Dry eye severity grading scheme was devised by the definition and classification subcommittee of the International Dry Eye Workshop in 2007. Besides ocular symptoms and signs, the scheme takes into account BUT and Schirmer I values to grade the severity of dry eyes.[6] BUT values of less than or equal to 10sec and Schirmer I value of less than or equal to 10mm are considered abnormal.[5,6,10]

Considering both eyes of the patients, the number of samples considered for statistical analysis was double the patient number.

The data were entered in Microsoft Excel 2007 worksheet and transferred to Statistical Package for Social Study (IBM® SPSS® Statistics 20) for statistical analysis. Demographics were analyzed using descriptive statistics whereas Paired Samples T test was used to compare the means. Pearson chi square value at 0.05 level of confidence was considered significant and at 0.001 level highly significant.

RESULTS

Fifty cases were included in the study. The mean age of the study group was 23.70 ± 4.381 years. The youngest patient was 16 years and eldest 33 years old. Among 50 patients, 30 (60%) were male and 20 (40%) female. Among the 30 male patients, 13 (43%) had severe nodulocystic acne and 17 (57%) had recalcitrant acne vulgaris, whereas among the 20 female patients, eight (40%) had severe nodulocystic acne and 12 (60%) had recalcitrant acne vulgaris. The mean weight of the participants was 58.60 ± 9.424.

Table 1. Tear break up time (BUT) in patients (n=50) receiving Isotretinoin for acne

Tear BUT (seconds)	Mean ± SD	p-value
Baseline	12.37±4.17	
At 45 days	9.69±3.70	0.000
At 90 days	9.09±3.77	0.004
Follow up	10.67±3.50	0.000

Table 2. Schirmer I test in patients (n=50) receiving Isotretinoin for acne

Schirmer I test (mm)	Mean ± SD	p-value
Baseline	16.68 ± 8.73	
At 45 days	12.26 ±7.64	0.000
At 90 days	11.49 ± 8.07	0.045
Follow up	11.76 ± 8.11	0.427

Table 3. BUT and Schirmer I at baseline and on follow up in patients (n=50) receiving Isotretinoin for acne

n=50	Baseline	Follow up	p-value
BUT (sec)	12.37±4.17	10.67±3.50	0.000
Schirmer I (mm)	16.68 ± 8.73	11.76 ± 8.11	0.000

DISCUSSIONS

In this study, the mean baseline value of BUT decreased significantly at 45 days and subsequently at 90 days but increased significantly thereafter on follow up. This is in accordance with the study done by Karalezli A et al[11] in which there were statistically significant differences in BUT values at baseline with that during, at the end and the follow up of oral Isotretinoin therapy. However, there is difference in the statistical analysis between the two studies. The current study compares the means at baseline with 45 days; 45 days with 90 days and 90days with follow up after 30 days, to elucidate the progression of decrease. When means at baseline and follow up were compared, the reduction in BUT was still statistically significant signifying that: even when BUT tends to increase after cessation of oral Isotretinoin, it does not reach the baseline value after one month. Cumurcu et al[12] also found dose dependent decrease in BUT values at 45 and 90 days of treatment with systemic isotretinoin.

There was statistically significant decrease in the mean Schirmer I value at 45 days and 90 days but no statistically significant decrease on follow up. However, there was marked statistically significant decrease on follow up compared with the baseline. Similar results were seen in the study by Karalezli A et al[11] in which Schirmer I values decreased significantly at 30 and 120 days of treatment with 0.8 mg/kg Isotretinoin compared with the baseline. Cumurcu et al[12] found that the decrease in Schirmer I values did not differ with dose of Isotretinoin. Mathers et al[13] and Bozkurt et al[14] who performed Schirmir II test on patients taking isotretinoin, did not find any statistically significant change before, during and after treatment. This is because Schirmer II indicates the volume of tears produced by lacrimal glands after irritation of the ocular surface whereas Schirmer I represents the basal tear secretion.[5,6]

Reports on the effect of isotretinoin therapy on production of the aqueous component of tears are not conclusive. Studies by Rismondo and colleagues demonstrate presence of Isotretinoin in lacrimal gland secretion of rabbits and humans. However, they concluded that it is not toxic to the lacrimal gland per se but its presence in the tear fluid may be related in part to its adverse ocular side effects.[15,16] The decrease in mean Schirmer I value during oral Isotretinoin therapy in this study and in the study by Karalezli A et al[11] could be due to the alteration of basal tear secretion by the presence of Isotretinoin and its metabolites in the tear film.

Though the mean values of Schirmer I decreased significantly in this study, it was never 10mm or less than that to label it as abnormal. On the other hand, mean BUT values at 45days and 90days were less than 10sec and were considered abnormal. DES is a clinical diagnosis. As clinical ocular findings were not taken into account, this study cannot conclude that oral Isotretinoin causes DES. However, with the findings of: 1) progressive decrease in mean BUT and Schirmer I values during oral isotretinoin therapy; 2) abnormal mean BUT while on treatment and; 3) slow increase in mean BUT and Schirmer I values after one month of its discontinuation; this study infers that oral Isotretinoin therapy for acne can cause DES. Larger studies considering the ocular clinical features as well as other diagnostic tests are required to further authenticate this statement. In day to day practice, artificial tears can be prophylactically prescribed during oral Isotretinoin therapy.[5,6]

Besides DES, oral isotretinoin can commonly cause conjunctivitis, hordeolum, chalazion, blepharitis, eye pain and more rarely, corneal opacities, decreased dark adaptation, decreased tolerance to contact lens, decreased vision etc.[4,23] Thus, patients undergoing oral isotretinoin therapy should be individualized and referred to an ophthalmologist when required.

CONCLUSIONS

Abnormal findings of BUT during this study concurs that DES can be induced by Isotretinoin. In this study, abnormal BUT values caused by Isotretinoin was not severe and tended to revert to baseline values after its discontinuation.

ACKNOWLEDGEMENTS

1. Dermatology department, Dhulikhel Hospital (Dr. Eliz Aryal Rajouria, Dr. Shekhar KC, all staff).
2. Ophthalmology department, Dhulikhel Hospital (Professor Dr. Bhagwat Nepal, Dr. Purnima Sthapit, Dr. Pooja Shrestha, Dr. Nirsara Shrestha, Mr. Rajan Kaiti).
3. Statistician, Dhulikhel Hospital (Mr. Sheshanada Sanjel).

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