The effect of systemic isotretinoin dose on dry eye parameters in patients treated from acne vulgaris

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Abstract: Purpose: To assess the effect of systemic isotretinoin dose on dry eye parameters in patients treated from acne vulgaris. **Patient and Methods:** Forty patients with different types of acne vulgaris treated with a dose 0.5mg/kg/day or 1mg/kg/day according to severity and response to treatment for six months. Ophthalmological assessment was done before treatment, 3 months and 6 months of treatment, and this included: tear break uptime, schirmer test, corneal fluorescein staining. **Results:** Our study revealed statistically significant affection of dry eye parameters (pvalue<0.05). **Conclusion:** There is a strong association between isotretinoin therapy and the development of obvious ocular side effects in the form of dry eye disease that can be controlled with careful follow up, but still safe with minimal difference in side effects between high and low doses.
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1. Introduction

Acne vulgaris is one of the most common disorders for which patients seek dermatologic care. Acne is a chronic inflammatory disease of pilosebaceous unit, clinically characterized by comedones, papules, pustules, nodules, cysts and in some cases scarring. It is the most common dermatological disorder affecting approximately 85% of individuals between 12- 24 year of age ***(Thiboutot and Strauss, 2003)*.**

Oral retinoids (isotretinoin) are the most effective drugs available for severe acne and many disorders of cornification ***(Thielenand Saurat, 2012)***. Isotretinoin (13-cis retinoicacid) has been approved by the Food and Drug Administration (FDA) for the treatment of cystic and nodular acne, which is not responsive to other forms of treatment ***(Yuksel et al., 2015).*** Retinoids exert their effect through cell proliferation, lipid synthesis and keratin expression. It suppresses sebum production up to 90% by inhibiting sebaceous lipid synthesis ***(Zouboulis and Orfanos, 2000).***

The usually prescribed dosage of isotretinoin starts with 0.5 to 1 mg/kg daily, divided in two doses. After 1 month of treatment with oral isotretinoin, the dosage should be adjusted according to clinical response and level of tolerance to the treatment. The usual duration of treatment varies between 15 and 20 weeks, with a total cumulative treatment dose of 120 to 150 mg/kg **(*Rigopoulos et al., 2010).*** Lower doses yield a favorable side effect profile, improve patient compliance, and a lower cost. However, high relapse rates are associated with a lower daily dose, and with a lower cumulative total dose (***Brelsford and Beute, 2008***).

It is a far safer compound but sometimes can cause serious side effects**.** Some of the most common ones are dryness of skin, lips, mouth and nasal mucosa. Other side effects are facial or body rash, itching, epistaxis, cheilitis, bleeding and inflammation of gums, easily injured skin and increased fatigue, depression. Teratogenic potential necessitates cautious use in females of child bearing age ***(Amichai et al., 2006).***

Ocular adverse effects associated with isotretinoin use have been reported, resulting mostly from changes to the eyelids and the surface of the cornea or lacrimal abnormality that leads to dry eye ***(Neudorfer et al., 2012).*** Blepharoconjunctivitis and dry eye symptoms are the most common and occur in 20%–50% of the patients usually at the third to fifth weeks of therapy. Meibomianitis, contact lens intolerance, blurred vision, photodermatitis of the eyelids, corneal opacities, papilledema, and pseudotumor cerebri were reported ***(Cumurcu et al., 2009)***.

The tear film is dynamic and synergistic with the cornea and conjunctiva. The lipid layer is the external one, and it is produced by Meibomian glands. Its function is to delay the evaporation of the lacrimal film. The aqueous layer is the major one. It is produced by the lacrimal glands and has high aqueous content. (***Valim et al., 2015)***. Meibomian Gland Dysfunction result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease ***(Foulks et al., 2003).***

Because there are similarities between the meibomian gland in the eye and the sebaceous glands in the skin, it has been suggested that isotretinoin might adversely affect the function of the meibomian glands ***(Karalezli et al., 2009)***. Keratitis, corneal opacity, corneal ulceration, and keratoconus. This occurs due to affection of the precorneal tear film that plays an important role in corneal stability and integrity ***(Fraunfelder, 2004).***

2. Patients and methods:

Full history was taken including age, sex, occupation, and family history of same disease. Full examination to determine type of acne. Adjustment of dose of systemic isotretinoin according to severity of acne and body weight of the patient. Patients with severe acne vulgaris or acne conglobate were treated with a dose 1mg/kg/day. Patients with moderate acne vulgaris were treated with a dose 0.5mg/kg/day or 1mg/kg/day according to response to treatment.

We excluded patients with Pregnancy and lactation, Patients with systemic hypertension, coronary artery disease, familial hyperlipidemia, diabetes mellitus, renal or hepatic functional disorders, severe osteoporosis or severe pulmonary, gastrointestinal, or hematologic problems.

A complete bilateral ophthalmologic examination was performed by the same ophthalmologist before the onset of treatment, at 3 months and 6 months of treatment. The examination included, external eye examination , corneal fluorescein staining, Schirmer test (drop of topical anesthetic agent (0.4% benoxinate hydrochloride) was instilled into the inferior fornix of the right eye and excess moisture on the eyelid margin was dried with a cotton tip applicator. A Schirmer test strip (Sno strips, Chauvin Pharmaceuticals Ltd.) was placed at the inferotemporal conjunctival fornix.) After 5 minutes the amount of wetting was measured in millimeters and recorded as the basal secretion. Wetness extending less than 10 mm on the test paper in 5 minutes was regarded as abnormal. Tear film break-up time (BUT) with 0.125% fluorescein solution absorbed strips (Fluo strip, India) applied to the lower conjunctival fornix and thereafter observing the tear film using the cobalt blue filter of the slit lamp. All values of 10seconds or less were considered abnormal. Patients were examined monthly for evaluation of treatment response, evaluation of ocular, cutaneous, systemic side effects, and management of them. During the treatment and follow-up periods.

3. Results:

Forty two patients were diagnosed with acne vulgaris, treated with systemic isotretinoin, 40 patients completed the study. (8 males, 32 females). 50% of the patients received systemic isotretinoin at a dose of 0.5mg/kg/day and 50% at a dose of 1mg/kg. Patients received treatment for 6 months. Thirteen patients (32.5%) and 19 patients (47.5%) had punctate epithelial erosions on corneal fluorescein staining at 3 and 6 months of treatment respectively. There was statistically significant difference in corneal fluorescein staining findings in the 3rd and 6th months of treatment compared with baseline values (p-value <0.05). Thirty three patients (82.5%) and 40 patients (100%) had abnormal decrease in BUT at 3 months and 6 months of treatment respectively. Eight patients (20%) and thirteen patients (32.5%) had abnormal decrease in schirmer test at 3 months and 6 months of treatment respectively (P-value <0.05). Based on the dose of systemic isotretinoin, the patients were divided into 2 groups: Group 1 (0.5 mg/kg/day); Group 2 (1 mg/kg/day). At 6 months of treatment, 9 patients of group 1 (45%) had punctate epithelial erosions (PEE) while 11 patients (55%) of group 2 had PEE. The mean BUT value was 5.2 sec ± 2.1 and 4.7 sec ± 1.9 in group 1 and 2 respectively at 6 months of treatment. Although changes in dry eye parameters results were higher among patients on high dose, but still statistically not significant with (p-value >0.05).

4. Discussion:

The aim of this study was to assess the ocular side effects in relation to the dose of systemic isotretinoin in patients treated for acne vulgaris. 32 patients were not symptomatic, and 8 patients suffered indoor symptoms in the form of burning, blurred vision and tearing. Three patients experienced these symptoms indoor and outdoor. Systemic isotretinoin was given in a dose of 0.5 -1 mg /kg/day for 6 consecutive months. The dose was adjusted according to the severity of acne and the response to treatment. Other authors used similar dosage protocols. ***Cumurcu et al., (2009)*** used systemic isotretinoin in a dose <0.5mg/kg /day for group (1) and a dose >0.5 mg /kg /day for group (2) **Aragona et al.*, (2005)*** used a dose of 0.5 mg/kg. In this study anaesthetized schirmer test showed statistically significant reduction in value with a mean value of 19.4±1.3 before treatment and 14.2±3.5 after treatment. This is similar to the findings of ***Cumurcu et al., (2009)*** with a mean value of 20.23±8.0 before treatment and 13.31±5.97 after treatment. This is also similar to ***Yildirim et al., (2014)*** with a mean value of 18.74 ± 3.42before treatment and14.92 ± 3.22 after treatment. On the other hand ***Aragona et al., (2005***) and ***Caglar et al., (2016)*** reported no changes in schirmer 1 test (non-anaesthetized) readings through out treatment. This may be due to using a schirmer 1 test which measures the volume of tears produced after irritation of the ocular surface by the presence of filter.

In this study tear BUT was significantly reduced after 6 months of treatment with mean of 14.6±3, and 4.9±2sec before and after treatment respectively. This is similar to the findings of ***Cumurcu et al., (2009)*** with a mean value of 15.23±4.95sec and 10.19±4.18 sec before and after treatment respectively for group A, and a mean value of 15.60±4.55sec and 14.88±4.33sec before and after treatment respectively for group B treated with low dose.

In our study corneal fluorescein staining revealed punctate epithelial erosions in about 47.5% which was statistically significant. On the other hand, ***Santodomingo-Rubido et al., (2008)*** reported a single case with minimal corneal staining. In our study there was no statistically significant difference in ophthalmological tests findings between patients received high dose isotretinoin and those who received low dose. This is similar to the findings of ***Cumurcu et al., (2009)***. Our study results suggest that ocular changes during the treatment are reversible and there is no permanent damage occurring to the eye.

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