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# Systemic Isotretinoin for the Management of Refractory and Recurrent Hordeolum in Blepharitis

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**Abstract.** Internal hordeolum is purulent eyelid infection arising from meibomian gland secondary to occlusion of the gland orifice by sebum or ductal hyperkeratinization. Recurrent and relapsing hordeolum cases in spite of current treatment modalities born out an idea of a new therapeutic agent focusing on the pathogenesis of hordeolum. Isotretinoin may be this agent with proven effects of inhibiting sebum production and ductal keratinization in pilosebaceous unit. The common developmental origin of the meibomian gland and pilosebaceous unit is the basis of our hypothesis that isotretinoin could inhibit the hordeolum formation. We suggest that similar act of mechanism of isotretinoin on acne vulgaris – the inflammatory disorder of the pilosebaceous unit – could be applied on meibomian glands and prevent hordeolum formation.

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## 1. Background

Blepharitis is one of the most common external eye disease encountered in daily ophthalmology practice. The term blepharitis includes conditions that result from pathology associated with the anterior lid and the meibomian glands of the posterior lid. Chronic inflammation of the eyelids including skin, lashes and meibomian glands can lead to a wide range of ocular discomfort complaints and furthermore sight threatening ocular surface disorders in untreated cases [1]. Blepharitis is not a uniform disease and classified basically as anterior and posterior on the basis of an anatomic landmark –the mucocutaneous line- of the lid margin. Sole involvement of the anterior lamella is generally due to staphylococcal infection and/or seborrheic dermatitis [2]. The focus of this article is posterior blepharitis which is mainly an issue of meibomian glands and could be described as obstruction, secretory anomalies and inflammation of meibomian glands [3,4]. Lid margin examination reveals telangiectasia, hyperemia, plugging and cysts on the meibomian gland orifices and foamy secretion in posterior blepharitis.

Internal hordeolum is an acute staphylococcal infection of clogged meibomian gland and may be a frequent component of posterior blepharitis. This painful and bothersome complication of meibomian gland obstruction may be recurrent and multiple in severe forms of blepharitis. The acute treatment consists of warm compresses with light massage over the lesion and rarely systemic antibiotics, however preventive efforts in recurrent cases are more challenging than acute therapy. Prevention of hordeolum is meant to treat the blepharitis. The conventional management of posterior blepharitis consists of warm compresses, lid hygiene, artificial tears, topical antibiotics and steroids. Systemic antibiotics especially tetracyclines are considered as second line treatment in severe, resistant cases. In spite of the mentioned intensive treatment modalities, relapsing recurrent hordeolum may constitute a troublesome group of patients. A

new therapeutic agent that will contribute to solve this problem would be helpful for both the ophthalmologists and the patients. Isotretinoin – a promising therapeutic in dermatology- might be this assumed agent when its act of mechanism in acne vulgaris and the similarity between the pathogenesis of acne vulgaris and hordeolum is taken into consideration.

## 2. Hypothesis

Oral isotretinoin may be an effective alternative in the management of relapsing and recurrent hordeolum related to the recalcitrant posterior blepharitis unresponsive to conventional treatment modalities especially in the forms of obstructive meibomian gland pathology. The rationale behind the use of systemic isotretinoin in the management of hordeolum is inhibiting the occlusion of meibomian gland orifices either by keratin or sebum plugging thereby inhibiting the first step of gland infection and inflammation.

## 3. Evaluation of Hypothesis

Isotretinoin (13-cis-retinoic acid), is a synthetic derivative of vitamin A acid (retinol) has been a vital medication in dermatologic disorders particularly acne vulgaris and in several disorders of keratinization for more than two decades [5]. The idea of its being a potential drug for hordeolum in posterior blepharitis is aroused from its proven effects in severe acne which may constitute an appropriate model for hordeolum pathogenesis.

Acne vulgaris is a self-limited inflammatory disorder of the pilosebaceous unit, that primarily affects adolescents [6,7]. The heterogeneous clinical features of acne including inflammatory and non-inflammatory lesions underlies a multifactorial pathogenesis [6,7]. The four basic steps considered important for the development of acne are; (i) ductal follicular hyperkeratinization, (ii) increased sebum production, (iii) inflammation, and (iv) the presence of *Propionibacterium acnes*

colonization [6]. Though these steps are entangled in each other follicular hyperkeratinization leading to comedogenesis is considered as the primary step in acne pathogenesis. Hyperproliferation of ductal keratinocytes, inadequate separation of the ductal corneocytes or a combination of both factors leads to comedogenesis due to the accumulation of corneocytes in the pilosebaceous duct [8]. It is shown that abnormalities of the sebaceous lipids such as increased free fatty acids, squalene and squalene oxide as well as a decrease in sebaceous linoleic acid, could all trigger hypercornification. Increased sebum production is likely an adjunctive phenomenon associated with the development of acne that mainly provides an anaerobic, lipid-rich follicle in which *P. acnes* can proliferate [7]. Retinoids, both oral and topical, are able to suppress comedogenesis [8]. Isotretinoin is the only retinoid with profound inhibitory effects on sebum production among all natural and synthetic retinoids, and this sebostatic effect is felt to account for its efficacy in severe acne [9-11]. Isotretinoin is also the unique anti-acne agent available in both the topical and oral forms that primarily or secondarily affects all four steps implicated in the pathogenesis of acne [10,11].

Meibomian glands are considered as large sebaceous glands of the eyelids embedded in the tarsal plate with an exception as the former is not associated with a hair follicle [12]. Both are sebum producing epithelial cells that release their content by rupture of the cell membrane and cellular degradation (holocrine secretion). It also has been demonstrated that meibomian gland development starts with the formation of an epithelial placode similar to that observed for the development of the pilosebaceous unit [13]. Meibomian gland obstruction is the leading factor in the pathogenesis of hordeolum. Ductal hyperkeratinization and/or thickening of the lipid secretion are the major causes of this obstruction similar to acne pathogenesis [14].

Isotretinoin, is shown to reduce sebaceous gland size by decreasing proliferation of basal sebocytes, suppressing sebum production up to

90% by inhibiting sebaceous lipid synthesis, and prohibiting the progression of sebocyte differentiation [15]. This act of mechanism may also be applicable to hordeolum in posterior blepharitis and similar results of therapy may be expected on meibomian glands.

Experimental studies concerning the effects of isotretinoin on meibomian glands were performed in animal models. In rabbits and hamsters treated with oral isotretinoin reported histopathologic findings of the meibomian glands were marked reduction in the size of the meibomian glands, decrease in the number and size of acini and the basaloid cells lining the acini walls [16-18]. These suggest that isotretinoin may regulate the secretory anomalies of the meibomian glands by suppressing the secretions and also inhibit pluggings that lead to hordeolum formation in posterior blepharitis.

Isotretinoin has several well known side effects which are usually dose dependent and reversible. Though, patients taking isotretinoin may develop potentially serious problems affecting a number of organs, including the liver, intestines, eyes, ears, and skeletal system. Beyond these, potential teratogenicity and mental health problems like psychosis and suicidal thoughts are the most striking ones [19]. The most frequent adverse effects involve mucocutaneous tissues and include cheilitis, xerosis, xerostomia, dry nose, epistaxis, and pruritus which are usually well tolerated by the patients [19]. Adverse ocular side effects secondary to isotretinoin are abnormal meibomian gland secretion, blepharoconjunctivitis, corneal opacities, decreased dark adaptation, decreased tolerance to contact lens, decreased vision, increased tear osmolarity, keratitis, meibomian gland atrophy, myopia, ocular discomfort, ocular sicca, photophobia, and teratogenic ocular abnormalities [20].

Although using a drug which is a cause of blepharitis itself for the prevention of posterior blepharitis complication appears to be a contradiction actually it's not like that at all. Isotretinoin induced blepharoconjunctivitis is a mucocutaneous side effect like cheilitis. Described

findings with isotretinoin use are crusting, redness, dryness of the lid and these resembles an involvement of the anterior lamella (skin) of the eyelid causing blepharitis. Furthermore no histopathologic evidence of acute or chronic inflammatory reaction of meibomian glands was noted in animal models receiving isotretinoin [17]. These are all against this contradiction as isotretinoin's side effect is anterior blepharitis and our target is meibomian glands which are component of posterior eyelid.

In summary, we propose oral isotretinoin may be a promising therapeutic agent for relapsing recurrent hordeolum related to the recalcitrant posterior blepharitis. Our hypothesis leans on the close similarity of acne vulgaris and hordeolum in respect to their pathogenesis. We believe further observations on case control studies will clarify the possible therapeutic effect and safety profile of oral isotretinoin on prevention of refractory and recurrent hordeolum.

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