Effectiveness Of Tacrolimus eye ointment for management of chronic vernal keratoconjunctivitis

Protocol of a thesis
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BY

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INTRODUCTION

Vernal keratoconjunctivitis (VKC) is a severe form of chronic, bilateral, allergic conjunctivitis that affects the ocular surface.[1]

Epidemiological studies do not consider it as a seasonal disease since frequently this persists throughout the year with increase intensity in warmer weather.[2]

VKC affects children between 3 and 16 years of age, though it may appear earlier and continue into adulthood. In most cases, symptoms resolve at puberty and the prevalence is more in males.[3]

The disease manifests in three forms: tarsal, limbal, and mixed. Symptoms include burning sensation, itching, perceived redness, watering, and photophobia, with associated lid swelling. Signs include tarsal papillae, Horner-Trantas dots, punctate epithelial keratitis and epithelial defects, shield ulcers, and pseudogerontoxon. Active shield ulcers, severe annular limbal inflammation, limbal stem cell deficiency manifesting as extensive conjunctivalization, limbal scarring, and extensive corneal scarring are blinding complications. Sequelae include tarsal scarring, dry eyes, and eyelid malpositions.[4]

Although the pathogenesis of this disease is still unknown, recent findings have shown it to be complex, involving T helper cell 2 (Th-2) lymphocytes, mast cells, eosinophils, fibroblasts, and cytokines in the inflammatory process.[5]

Topical medication for the treatment of VKC includes antihistamines, mast-cell stabilizers, corticosteroids, and immunomodulator drugs. The efficacy of antiallergic agents is good for symptom relief but poor for reversing papillary hyperplasia in the eyelid. The use of ocular steroids is effective in the treatment of VKC, but injudicious and prolonged use often leads to complications such as glaucoma, cataracts, and secondary infections.[6] To prevent steroid-related complications, immunomodulatory agents such as topical tacrolimus are now being to treat VKC.[7,8]

Tacrolimus, derived from the bacterium Streptomyces tsukubaensis , like cyclosporine, is a calcineurin inhibitor in the immune mechanism but with a 100-fold-greater potency.[3] It suppresses Th2 lymphocyte activation, Th cell-mediated B cell proliferation, and the formation of cytokines. Tacrolimus also inhibits histamine release from mast cells, thought to alleviate allergic symptoms. It was initially used as an immunosuppressant in liver transplantation but was subsequently introduced for other solid-organ transplants over several decades.[9]

Ophthalmology studies have demonstrated that topical tacrolimus (0.02–0.1%) ointment is effective in the treatment of giant papillary conjunctivitis, atopic keratoconjunctivitis (AKC), and VKC. [10,11]

So the purpose of this study is to study the effectiveness of topical Tacrolimus ointment for treatment of chronic vernal keratoconjunctivitis in comparison to a control group taking topical corticosteroids as a traditional treatment.

AIM OF THE WORK

The aim of this study is to study the effectiveness of Tacrolimus eye ointment for treatment of chronic Vernal Keratoconjunctivitis.

OBJECTIVES

- **Primary objectives**

To evaluate the effectiveness of topical Tacrolimus eye ointment for treatment of chronic vernal keratoconjunctivitis in comparison to a control group taking topical corticosteroids as a traditional treatment.

- **Secondary objectives**

1. To evaluate the changes in symptoms and signs after treatment in two groups.
2. To evaluate bulbar conjunctiva, cornea and palpebral conjunctiva as treatment progress by using anterior segment OCT.

STUDY QUISTION

Is the use of topical tacrolimus ointment is effective in treatment of chronic vernal keratoconjunctivitis ?

PATIENTS AND METHODS

- **Type of the study:**

  Intervention , Quasi-Experimental study.

- **Setting of the study:**

  Damietta Ophthalmology Hospital, Damietta, Egypt.

- **Study population:**

Fifty patients with chronic VKC will be randomized into two matched groups first group will be treated with tacrolimus eye ointment and the second control group will be treated with traditional treatment (Topical corticosteroids eye drops and ointment).

- **<u>Inclusion criteria:</u>**

1. All new and previously untreated cases of VKC (palpebral, limbal or mixed type).
2. Cases that developed steroid- related complications such as glaucoma or cataract , in control group, will be treated.

- **Exclusion criteria:**

1. patients younger than 3 years.
2. History of contact lens usage.
3. Past history of ocular surgery or herpes infection.
4. Patients with co-existing ocular diseases like corneal infections, corneal dystrophies, chemical injuries, Steven Johnson syndrome and uveitis.
5. Patients under VKC remission.
6. History of systemic immunosuppressive drug use.

- **Methods:**

- All included patients that will be diagnosed with VKC will receive comprehensive ophthalmic examinations at each visit, including:

1. Estimation of best-corrected visual acuity.
2. Slit-lamp examination.
3. Fluorescein staining.
4. Measurement of intraocular pressure.
5. Fundoscopy.

- Fifty patients with chronic VKC will be randomized into two matched groups first group will be treated with tacrolimus eye ointment and the second control group will be treated with traditional treatment (fluorometholone eye drops and dexamethasone eye ointment).
- First group will receive tacrolimus 0.03% ointment (Tacliment 0.03%; Aurolab, Madurai, India). Twice daily for 2 months and then once daily for 2 months followed by once every other day for 2 months.

- Second group (control group) will receive topical fluorometholone 0.1% eye drops (Flucon; Novartis Pharma AG, Basel, Switzerland) 3times daily for two weeks and tobramycin 0.3% + dexamethasone 0.1% eye ointment (Tobradex Ophthalmic Ointment; Novartis Pharma AG, Basel, Switzerland). Treatment withdrawn gradually from control group after two weeks, if symptoms disappeared ,maintenance on topical olopatadine 0.1% (Patanol; Novartis Pharma AG, Basel, Switzerland) three times daily during follow up period, if exacerbation occurred corticosteroid will be used again.
- Disease severity will be assessed based on a four-point scale of symptoms and signs (Table 1,2).[4]
- The composite score of symptoms and signs will be made at the time of enrollment and subsequent follow up visits at 1 week, 1 month, 3 months and 6 months.
- The primary measure of treatment effectiveness will be a lower final score of objective signs.
- By using anterior segment Optical coherence tomography (OCT) we will measure conjunctival papillae (horizontal &vertical) and thickness of conjunctiva at the limbus pre-treatment, at 3 months and at 6 months post treatment as a objective measure to assess improvement and treatment effectiveness and correlate it with the resolution of symptoms and signs.[12]
- The follow up will depend on the severity of the disease but all the patients will be assessed in 1 week, one month, 3 and 6 months of treatment.

Table 1. Score for clinical symptoms.[4]

Symptoms and severity	**Score**
• **Burning**	
Absent	0
Mild	1+
Moderate	2+
Severe	3+
• **Discharge**	
Absent	0
Mucoid discharge in the lower cul-de-sac	1+
Moderate	2+
Matted lids requiring frequent cleaning	3+
• **Itching**	
No need to itch	0
Occasional itching	1+
Frequent itching	2+
Constant itching	3+
• **Photophobia**	
Absent	0
Sensitivity to sunlight but can open eyes	1+
Sensitivity/intolerance to sunlight: eyes cannot be kept open for long	2+
Intolerance to sunlight: avoidance and inability to open eyes	3+
• **Perceived redness**	
Absent	0
Detected only on close observation	1+
Detectable at near	2+
Detectable at distance	3+
• **Watering**	
Normal tear production	0
Waterlogged feeling	1+
Infrequent spilling of tears	2+
Constant spilling of tears	3+

Table 2. Score for clinical signs.[4]

Clinical signs and severity	**Score**
• **Conjunctival fibrosis**	
No scar	0
Sub epithelial fibrosis	1+
Fornix shortening	2+
Symblepharon	3+
• **Conjunctival hyperemia**	
Absent	0
Dilation of some blood vessels (1 quadrant)	1+
Dilation of several blood vessels (›1 quadrant)	2+
Generalized dilation of blood vessels	3+
• **Horner-Trantas dots**	
None	0
1-3	1+
4-6	2+
› 6	3+
• **Limbal inflammation**	
None	0
1 quadrant	1+
2 quadrants	2+
3-4 quadrants	3+
• **Punctate keratopathy**	
Intact epithelium	0
Punctate in 1/3 of cornea	1+
Punctate in 2/3 of cornea	2+
Diffuse punctate	3+
• **Tarsal papillary reaction**	
No papillae	0
Papillary reaction without giant papillae	1+
Some giant papillae	2+
Giant papillae all over the tarsal conjunctiva	3+

Study sample size:

The number of patients:

The sample size will be calculated using the following formula[13]:

$$n = 2\left[\frac{\left(Z_{\alpha/2} + Z_{\beta}\right) * \sigma}{\mu_1 - \mu_2}\right]^2$$

Where:

n = sample size

$\mathbf{Z_{\alpha/2}}$ = 1.96 (The critical value that divides the central 95% of the Z distribution from the 5% in the tail)

$\mathbf{Z_{\beta}}$ = 0.84 (The critical value that separates the lower 20% of the Z distribution from the upper 80%)

σ = the estimate of the standard deviation = 0.6

$\mathbf{\mu_1}$ = Mean scores of papillae after four weeks in the post-intervention group = 1.4

$\mathbf{\mu_2}$ = Mean scores of papillae in the pre-intervention group = 1.9

So, by calculation, the sample size will be equal to 23 patients.

The expected drop-out is 10% so it will be 2-3 person in each group.

STATISTICAL ANALYSIS

Gathered data will be processed using SPSS® version 16.0.1 (SPSS Inc., Chicago, IL, USA) statistical package for Windows®. Quantitative data will be expressed as means ±SD while qualitative data will be expressed as numbers and percentages (%). Student t test will be used to test significance of difference for quantitative variables and Chi Square will be used to test significance of difference for qualitative variables, a probability value (p-value) < 0.05 will be considered statistically significant.

ETHICAL CONSIDERATIONS

1. Full consent will be obtained from the participants prior to the study.

2. Patients will be informed about any abnormal results of procedures and will be instructed and treated accordingly.

3. The patients have the right to refuse participation without affecting the medical care expected to be offered to the patient.

4. Confidentiality of all data and results of all study population will be preserved.

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الملخص العربي

المقدمة

الرمد الربيعي هو شكل حاد من التهاب الملتحمة المزمن التحسسي الذي يصيب كلتا العينين. كما أن الدراسات الوبائية لا تعتبره مرضًا موسميًا لأنه يستمر طوال العام مع زيادة شدته في الطقس الدافئ.

يصيب الرمد الربيعي الأطفال الذين تتراوح أعمارهم بين 3 و 16 عامًا ، و قد يظهر مبكرًا ويستمر حتى سن الرشد وفي معظم الحالات تختفي الأعراض عند سن البلوغ وينتشر المرض بشكل أكبر عند الذكور .

أعراض الرمد الربيعي تشمل حرقان بالعبن وحكة واحمرار مع زيادة افراز الدموع والحساسية المفرطة للضوء وقد تؤدي الى حدوث بعض المضاعفات مثل القرنية المخروطية وقرحة مزمنه بالقرنية.

الأدوية الموضعية لعلاج الرمد الربيعي تشمل مضادات الهيستامين ، ومثبتات الخلايا البدينة ، والكورتيزون ، والادويةً المعدلة للمناعة. فعالية العوامل المضادة للحساسية جيدة لتخفيف الأعراض ولكنها ضعيفة في علاج تورم الجفن. إن استخدام الكورتيزون فعال في علاج الرمد الربيعي، لكن الاستخدام المفرط غالبًا ما يؤدي إلى مضاعفات مثل الجلوكوما ، والمياه البيضاء. ولمنع هذه المضاعفات المرتبطة بالكورتيزون ، يتم الآن استخدام الأدوية المعدلة للمناعة مثل التاكروليمس الموضعي .

إن عقار التاكروليمس يمنع إطلاق الهستامين من الخلايا البدينة ، ويعتقد أنه يخفف من أعراض الحساسية. وقد تم استخدامه مبدئيًا كمثبط للمناعة في زراعة الكبد. وقد أثبتت الدراسات التي أجريت فعاليته في علاج مجموعة من حالات العيون مثل التهاب الملتحمة الحليمي العملاق والرمد الربيعي.

الهدف من البحث

الهدف من هذه الدراسة هو الحصول على علاج آمن وفعال للمرضى الذين يعانون من الرمد الربيعي المزمن.

خطة البحث

المرضى

سوف يتم اجراء هذه الدراسة على ٥٠ مريض تم اختيارهم عشوائيا من:

1. جميع حالات الرمد الربيعي الجديدة وغير المعالجة سابقًا.
2. الحالات التي حدث لها مضاعفات نتيجة الكورتيزون تحول لمجموعه التاكروليمس.

وسوف نستبعد من هذه الدراسة:

1. المرضى الذين تقل أعمارهم عن 3 سنوات.
2. المرضى الذين قد سبق لهم استخدام العدسات اللاصقة.
3. المرضى الذين لهم تاريخ مرضي من اجراء عمليات جراحية بالعين أو عدوى فيروس هربس.
4. المرضى الذين يعانون من أمراض عين مثل عدوى بالقرنية ، والإصابات الكيميائية ، ومتلازمة ستيفن جونسون والتهاب القزحية.
5. المرضى الذين يستخدمون الادوية المثبطة للمناعة.

❖ **و سوف يتم إخضاع المرضى للآتي:**

- ✓ أخذ التاريخ المرضي.
- ✓ فحص كامل للعين.
- ✓ سيتم تقسيم المرضى الى مجموعتين المجموعه الأولى سيتم إعطاؤها مرهم موضعي تاكروليمس ٠,٠٣٪ مرتين يوميًا لمدة شهرين ثم مرة واحدة يوميًا خلال الشهرين التاليين ثم مرة كل يومين لمدة شهرين آخرين والمجموعة الثانية سوف يتم اعطاؤها العلاج التقليدي من خلال قطرة ومرهم الكورتيزون.

- ✓ سيتم تقييم التغييرات في الأعراض بعد بدء العلاج وأيضًا تقييم المضاعفات المحتملة في كل متابعة.
- ✓ سيتم عمل اشعة مقطعية على الملتحمة قبل وبعد العلاج لقياس مدى التحسن وفعالية العلاج.
- ✓ تعتمد المتابعة على شدة المرض ولكن سيتم تقييم جميع المرضى بعد أول أسبوع من العلاج ثم بعد شهر و 3 و 6 أشهر من العلاج.

فعالية مرهم التاكروليمس للعين في علاج الرمد الربيعي المزمن

خطة بحثية مقدمة إلى كلية الطب جامعة بورسعيد إستيفاءا لمتطلبات الحصول على درجة الدكتوراة في تخصص طب وجراحة العين

مقدمة من

الطبيب/ محمود محمود التاجوري

ماجستير طب وجراحة العين

اخصائي **طب وجراحة العين**

مستشفى **طب وجراحة العين بدمياط**

المشرفون

أ.د/ إيهاب محمود غنيم

أستاذ طب وجراحة العين

رئيس **قسم طب وجراحة العين**

كلية **الطب**

جامعة **بورسعيد**

أ.د/ وليد علي أبو سمرة

أستاذ طب وجراحة العين

مركز طب وجراحة العين

كلية **الطب**

جامعة **المنصورة**

كلية الطب

جامعة بورسعيد

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