Cilostazol reduces dry eye symptoms and improve walking distance in patients with peripheral artery disease

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Abstract

Aim of the study. Cilostazol is a phosphodiesterase III inhibitor that has anti-inflammatory and immunomodulatory effects and can act with beneficial effect in Dry Eye Syndrome (DES).

This clinical trial evaluates the effects of cilostazol on the tear film.

Materials and Methods. Following the run-in period, subjects were randomly into two groups: 40 subjects treated with cilostazol and 40 no-treated subjects.

The Walking Impairment Questionnaire (WIQ) has been administered to all patients.

Results. The data obtained from comparison of the two study groups A and B were, respectively, the following: Schirmer I: 10.2±0.2 Vs 13.8±0.4 (p< 0.001); Schirmer II: 3.8±0.1 Vs 4.6±0.2 (p<0.001); Break-up time (BUT) 4.2±0.3 Vs 6.5±0.2 (p<0.001) with disappearing of symptoms. The WIQ showed a significant difference in the walking distance (p<0.05) and calf pain severity (p<0.005) of treated patients.

In comparison with the placebo group, treated patients showed an improvement (p<0.03) in calf pain severity.


Key words: Dry Eye Syndrome (DES), cilostazol, peripheral artery disease, therapy ocular surface, intermittent claudication

Introduction

Approximately 40% of subjects affected with peripheral arterial disease complain of pain in the legs when walking, this is known as intermittent claudication.

Peripheral arterial disease (PAD) is very common in 20% of people over 70 years of age and in male population aged >50 years and affects 8 million people in the United States(1).

Leading risk factors include not only advanced age but also smoking, diabetes mellitus, hypertension, hyperlipidemia, hyperhomocysteinemia (2-6).

Dry Eye Syndrome (DES) is an inflammatory disease that has many features in common with autoimmune disease(7-9),

DES is characterized by discomfort, visual disturbance, constant irritation, foreign body sensation, and blurred vision (10-12).

DES impairs functional vision in reading at the computer or when driving (13-16).

Dry eye is often associated with peripheral artery disease (17-21).

The pathogenesis of DES has not been fully elucidated, however there is a growing body of evidence indicating that DES is an immune-mediated disorder (22, 23).

Elevated tear film osmolarity is thought to precipitate inflammation by activating intracellular stress-associated mitogen activated protein (MAP) kinase pathways that induce the production of pro-inflammatory cytokines (24, 25).

Anti-inflammatory and immunomodulatory medications, such as corticosteroid and cyclosporine are used clinically in the treatment of DES (26, 27).

Cilostazol is a phosphodiesterase-III inhibitor that has antiplatelets and antithrombotic actions(28). Cilostazol also acts on smooth muscle cells as a vasodilator with beneficial effects on triglycerides and high-density lipoprotein (HDL) (29).

Cilostazol is indicated for intermittent claudication, but there is also evidence to suggest that cilostazol may have a role in reducing both cardiovascular disease and vascular events (30-32).

Phosphodiesterases (PDEs) are involved in the regulation of numerous intracellular signal transduction pathways (33). The PDE family predominates in inflammatory cells and PDE inhibition is a promising method of potentially abrogating pathogenic inflammation.

This study evaluated the therapeutic potential of cilostazol in DES.

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**Materials and Methods**

**Study design**

This clinical trial was a pilot study to evaluate the effects of cilostazol in patients with PAD and DES versus a group of control subjects (Fig. 1).

All patients were treated with substitute tear film. Patients were randomly grouped to receive 100 mg of cilostazol or placebo for 12 weeks.

The study was approved by the Institutional Review Board of Science of Senescence of Catania University and was conducted in accordance with Declaration of Helsinki. Eligible subjects included were men and women aged 38-70 years.

**Patients**

All patients with clinical or pathologic evidence of DES and PAD in our department were invited to participate in the study: 40 as patients and 40 as control subjects. We collected all the demographic data, date of first symptoms and date of diagnosis (Table 2). None of the patients had had infections of the ocular surface or allergic diseases of the ocular surface in the 30 days preceding the start of the study. We excluded patients with current or previous ocular diseases, such as strabismus, cataract, glaucoma, or risks of developing seasonal allergy between May and September, allergy to the test supplement, previous eye surgery, lacrimal disorders, systemic or topical medications that alter the tearing and/or topical steroids during the 4 weeks preceding the start of the study. Other exclusion criteria were the use of any symbiotic product intended to improve gastrointestinal function within the 2 weeks preceding the start of the study; major chronic and uncontrolled systemic medical conditions and lactose intolerance.

In all patients, the subjective symptoms and objective signs at the time of enrolment visit and after 12 weeks of treatment were considered. Five days after cessation of treatment (washout), the clinical parameters were reassessed. At the end of treatment, five days after washout, all of the patients belonging to the two groups A (control) and B received Schirmer test I, II Schirmer test, BUT test and underwent bacteriological research. All patients with DSE were recruited and were admitted to the study: 43 females and 37 males, aged 65-78 years (Table 2) showing signs of dryness or itching.

**Methods**

The evaluation of the clinical signs of dry eye considers three features of the tears film and ocular surface: tear functions, tear composition, and ocular surface alterations. The simple tear function tests are performed by direct observation of all patients. The questionnaire (OSDI) had been administered to all patients. Tear film instability is an important sign of dry eye disease and can be produced by either aqueous-deficit dry eye, evaporative dry eye, or a combination of both mechanisms.

The method for determining tear film stability is the tear fluorescein in break-up time (TF BUT) that is performed by instilling a small amount of fluorescein dye into the tear film and having the patient blink while being observed through the slit-lamp with incident cobalt blue filtered light.

The uniform distribution hue of the fluorescein across the cornea is observed for early break-up as identified by a dark spot forming in the tear film. The normal TF BUT range is 10-15 seconds.

Rapid tear film break-up is an indicator of tear instability that can be due to dry eye or ocular surface irregularities. Determination of tear secretion rate differentiates aqueous-deficient dry eye from evaporative dry eye and is most frequently done clinically by use of the Schirmer tear test strip.

The Schirmer test is performed by placing a small strip of filter paper of a pre-determined dimension (5x35 mm) on the edge of the lower eyelid at the junction of the lateral and middle third of the lid and leaving it in place for 5 minutes, and then measuring the length of the strip that is wet with tears. This test is done without prior instillation of topical anaesthetic and it is a measure of reflex secretion of tears (Schirmer 1 test); if the test is done following instillation of a topical anaesthetic, it is a measure of baseline tear secretion (basal tear secretion test). The normal value of the Schirmer 1 test is greater than 10 mm of wetting, but cut-off referent values for dry eye have been recommended as 5 mm of wetting.

Some clinicians use a value of 7 mm with the Schirmer 1 test and 3 mm for the Schirmer with anaesthetics test (3-9-15-17).

**Walking Impairment Questionnaire**

The Walking Impairment Questionnaire (WIQ) is a validated and short questionnaire easy to complete and inexpensive. This questionnaire evaluates walking ability, with a focus on walking distance, walking speed and the ability to climb stairs.

Symptom scores ranged from 0% (patients unable to walk 20 feet without stopping to rest) to 100% (patients able to walk five blocks without stopping to rest) (2-16-19).

Stair climbing scores ranged from 0% (patients unable to climb 1 flight of stairs without stopping to rest) to 100% (patients able to climb 3 flights of stairs without stopping to rest) (34, 35).

**Safety parameters**

Safety parameters included blood tests (haemoglobin, haematocrits, white blood count and thrombocytes) and both renal and liver function tests before and after treatment.

**Statistical analysis**

The results are expressed as mean ± standard deviation. Statistical significance in contingency tables was evaluated using the Chi-Square and Fischer exact test. Student’s test for unpaired data, one-way ANOVA, and Mann-Whitney rank sum test were used for comparisons of continuous variables.
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Statistical analysis was performed using tests for repeated measures as well by controls for multiple comparisons with correction by Duncan’s Procedure.

Data were analyzed using the STATA V.11.0 software packages (StataCorp. 2011. Stata Statistical Software: Release 12. College Station TSL).

**Results**

**Baseline data**

Baseline subject characteristics were similar among the two treatment groups (Fig. 1). Frequency of consumption of food categories was, in general, similar across the treatment groups (Table 1).

![Flow chart of the study](image1)

![Break-up time in study group A (PAD) and group B (control)](image2)

![Schirmer's tests I and II in study group A (PAD) and group B (control)](image3)
Table 1. Demographic characteristics of patients (data values are described as Mean±SD).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Demographic characteristics</th>
<th>Group A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B Gender (M/F)</td>
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<td>18/22</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>45-60</td>
</tr>
<tr>
<td>Heart Rate (b.p.m.)</td>
<td></td>
<td>80.4±8.2</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td>150±12</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
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</table>

Table 2. Assessment of subjective Symptoms of Dry Eye and PAD.

<table>
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<th>Parameters</th>
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<th>Group B</th>
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<tr>
<td></td>
<td>Before (I Group)</td>
<td>After (II Group)</td>
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<tr>
<td>Foreign body sensation</td>
<td>Frequency</td>
<td>2.6±0.5</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>3.2±0.5</td>
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<tr>
<td>Dry sensation</td>
<td>Frequency</td>
<td>2.8±0.4</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>3.1±0.4</td>
</tr>
<tr>
<td>Pain or soreness</td>
<td>Frequency</td>
<td>3.1±0.6</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>2.3±0.6</td>
</tr>
<tr>
<td>Ocular fatigue</td>
<td>Frequency</td>
<td>3.1±0.6</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>2.7±0.6</td>
</tr>
<tr>
<td>Eyelid heaviness</td>
<td>Frequency</td>
<td>2.9±0.5</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>2.8±0.7</td>
</tr>
</tbody>
</table>

Frequency: 0 (none) – 4 (highest)
Severity: 0 (none) – 4 (highest)

Table 3. Groups comparisons p value

<table>
<thead>
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<th>Parameters</th>
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<th>Intergroupcomparison</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>I Vs II</td>
<td>III Vs IV</td>
<td>I Vs III</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>Frequency</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.326</td>
<td>p&lt;0.001</td>
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<tr>
<td>Dry sensation</td>
<td>Frequency</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>1</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Pain or soreness</td>
<td>Frequency</td>
<td>0.421</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.529</td>
<td>0.006</td>
</tr>
<tr>
<td>Ocular fatigue</td>
<td>Frequency</td>
<td>1</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Severity</td>
<td>0.421</td>
<td>p&lt;0.001</td>
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<tr>
<td>Eyelid heaviness</td>
<td>Frequency</td>
<td>0.374</td>
<td>p&lt;0.001</td>
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<tr>
<td></td>
<td>Severity</td>
<td>0.161</td>
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<tr>
<td>Eye redness</td>
<td>Frequency</td>
<td>0.464</td>
<td>p&lt;0.001</td>
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<tr>
<td></td>
<td>Severity</td>
<td>1</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
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Effect of cilostazol on DES

The data obtained in the two study groups A and B were, respectively, the following: Schirmer I 10.2±0.2 Versus 13.8±0.4 (p< 0.001); Schirmer II 3.8±0.1 Versus 4.6±0.2 (p<0.001); BUT 4.2±0.3 vs 6.5±0.2 (p<0.001). (Figure 2 and 3, Table 2-3).

Effect of cilostazol on WIQ

Through the WIQ, a significant difference in values of walking distance (p<0.01) and calf pain severity (p<0.01) were observed in cilostazol treated patients.

An improvement (p<0.05) in calf pain severity was observed in the treated patients in comparison with the placebo group (Table 5).

Discussion

Symptoms of intermittent claudication, walking distance and modification of risk factors, including smoking cessation, a structured exercise programme, and diet can improve the disease progression and prognosis.

Some drug therapies are used to help improve walking distance in patients suffering from intermittent claudication.

Smoking cessation, regular physical activity is the most effective non-invasive therapy to improve pain symptoms and amputation in intermittent claudication.

Patients with PAD treatment with cilostazol showed greater improvement in the walking impairment questionnaire and functional status than the placebo group.

Medication that modulates inflammation and immunity are of great interest in the treatment of DES. The significant change in tear testing (Schirmer I, II and Schirmer B.U.T.) obtained after treatment with cilostazol, with the disappearance of symptoms, showed a good activity in the physiological recovery of the ocular ecosystem in patients with DES. In recent years, most drugs used in cardiovascular diseases can affect the immune system. Cilostazol suppresses the differentiation of Th1 and Th17 cells (36). Since cilostazol can influence T cells, monocytes and macrophages and could inhibit the proliferation of antigen-specific T cells by downregulating the antigen presentation function, this may explain how cilostazol protects the tear film (37-40). Cilostazol also could inhibit Interferon alfa and Tumour Necrosis Factor alfa (TNF-alfa) and ameliorates experimental autoimmune disease (41-45).

The phosphodiesterase inhibitor cilostazol suppresses platelet aggregation and is a direct arterial vasodilator. Cilostazol has been shown to improve claudication symptoms and increase maximal and pain-free walking distances in patients with PAD compared with placebo (45-52) Many studies were performed for shorter periods, thus limiting a correct evolution of effectiveness, tolerability and adverse effects (53-55). We observed that both objective and subjective parameters were alleviated after treatment. The dry eye symptoms decreased significantly in the treated group compared to the placebo group (Table 3). These results indicate that cilostazol reduces the dry eye symptoms and severity.

A supervised exercise program would be composed of at least three walking session per week (30-60 minutes each) for a minimum duration of 12 weeks (53).

In the present study, no serious adverse effects were detected. The mechanisms involved in improvement of ocular surface are not known.

In subjects cilostazol treated we observed an increased Schirmer test values, reduced symptoms (blurry vision, ocular dryness, foreign body sensation and epiphora) and a reduction in the use of artificial tears. The clinical improvement was associated with a reduction in inflammatory cells and inflammatory marker in the ocular surface (54-56).

As has been demonstrated in previous research, the stable tear film is the result of the balance of a series of complex functions, implemented by the system of the ocular surface. An environment suitable for pH, electrolyte concentration, relative humidity, and presence of fundamental nutritive elements is indispensable for the ocular surface (57,58). Our findings indicate that cilostazol ameliorates DES as determined by clinical and inflammatory measures. Additional research is needed to demonstrate whether these results can be replicated and how long-lasting the benefits are.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.
References

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