BIOPTRON LIGHT THERAPY TO DRY EYE CAUSED BY LONG-TERM TOPICALLY APPLIED ANTIGLAUCOMA DRUG WITH BENZALKONIUM-CHLORIDE

Suzana Branković¹, Radica Dragojlović-Ružičić², Nataša Branković³, Marija Cvetanović⁴, Aleksandar Veselinović⁴

Benzalkonium-chloride is the most commonly used preservative in modern antiglaucoma topical therapy, with a broad range of advantages and cumulative side effects on the anterior eye surface. Benzalkonium-chloride is classified as a severe irritant of mucous membranes, resulting in dryness of the anterior eye surface.

The aim of the paper was a scientific confirmation of the efficacy of Bioptron light therapy, its favorable response in healing and elimination of dry eye symptoms and signs caused by topical use of antiglaucoma therapy with Benzalkonium-chloride as a preservative.

The research included 36 patients who were divided into three groups: the first and second group with different approaches in the treatment of dryness of anterior eye surface, and the third control group. A complete ophthalmic examination of the patients was done before our examination and after Bioptron light therapy. The examination was done according to „Dry eye severity grading scheme”, and as an objective parameter we did Shirmer’s test 1. In the second group of patients, cured by Hylo®gel solution and Bioptron light therapy, symptoms and signs decreased from 27.78% to 5.56% (< 0.001). The values of Shirmer’s test 1 showed an improvement from 30.56% to 13.89% deficit in tear secretion (< 0.001). The symptoms and signs of anterior eye surface dryness are statistically significantly reduced. Tolerance of antiglaucoma drug therapy, comfort and patient compliance are significantly improved. It is necessary to include Bioptron light therapy in all patients on antiglaucoma therapy with Benzalkonium-chloride as a preservative.


Key words: Benzalkonium chloride, Keratoconjunctivitis sicca, Bioptron® light therapy

Introduction

Modern antiglaucoma therapy includes a large number of different topically applied drugs (1). The presence of one of many preservatives in antiglaucoma eye drops is necessary because of their effects on preventing contamination of the eye drops by pathogenic microbes as well as decomposition of active drug on which their shelf-life depends. Different eye solutions may have important and dangerous cytotoxic effects of preservatives on corneal, limbal and conjunctival cells, and if they are associated, especially with long-term use, may cause an additive cytotoxic effect (2). The most frequently used preservatives in ophthalmic preparations are Benzalkonium chloride (BAK), Chlorobutanol, Poliquad®, Stabilized oxichloro complex (Purite), sodium perborate (Gen-Aqua™), SofZia™ ect. (3). Preservatives can have a negative effect on the structure of anterior segment of the eye. From toxicological standpoint, BAK is classified as a severe irritant of mucous membranes and skin (4). Its advantages lie in better penetration of active medication through tear film and cornea, limiting bacterial, viral, mycotic and amoeba infections, without biodegradation of the active medication at the same time. Side effects are cumulative cytotoxic effects on the front eye surface, tear layer disturbance, dry eye, and allergic reactions (5). Good penetration of the drug through the cornea is necessary because of the characteristics of the surfactant and dissolution of the lipid layer of the tear film (6). Its concentration in antiglaucoma drops is from 0.004% to 0.01%. Higher concentrations can cause

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irreversible damage to the corneal endothelium (7). The most important collateral effect of BAK is apoptosis and necrosis of corneal epithelium cells, changes of corneal permeability for active drug substance, emergence of tear film instability, dry eye occurrence, discomfort caused by inflammatory changes of conjunctival and subconjunctival fibrosis (8). These changes on the eye front surface are observed 10-15 days after the beginning of use of ophthalmic drops with BAK as a preservative. If side effects of BAK occur in dry eye field, changes are much more undesirable, according to our evidence (9). Symptoms of dry eye are stinging, burning, pain, redness and photophobia. “Dry eye severity grading scheme” distributes symptoms to four levels (Table 1). For conducting this clinical examination, it was necessary to test patient’s psychometric abilities (10). In diagnostic tests for dry eye, the quantity and quality of tear secretion was measured (Shirmer’s test) ( Tear Break up Time-test). Shirmer’s test is a first and simple method including Shirmer’s test 1 without anesthesia, where pathological values are ≤ 10 mm in 5 min, and Shirmer’s test 1 with anesthesia for basal tear secretion, with pathological values ≤ 8 mm in 5 min.

The symptoms of dry eye may decrease without therapy (11). They are more common in older patients, menopausal women, during the therapeutic use of drugs for systemic diseases, and can be the result of constant exposure to air conditioning, wind, dust; they occur in people with long-lasting work on the computer, in case of perennial contact lens holders, in conditions when it is impossible to fully close eyelids, rare blinking, and in cases of various lacrimal gland diseases (12). Normal secretion of a triple-layer in tear film structure serves for the general protection, moistening and nutrition for cornea (13).

Table 1. Dry eye severity grading scheme

<table>
<thead>
<tr>
<th>Dry eye severity level</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discomfort, frequency</strong></td>
<td>Mild, episodic symptoms</td>
<td>Moderate, occasional or chronic symptoms</td>
<td>Severe frequent or constant symptoms</td>
<td>Severe, disabling, constant symptoms</td>
</tr>
<tr>
<td><strong>Visual symptoms</strong></td>
<td>None or episodic mild fatigue</td>
<td>Annoying, activity-limiting</td>
<td>Annoying chronic and constant, activity-limiting</td>
<td>Constant, disabling</td>
</tr>
<tr>
<td><strong>Conjunctival injection</strong></td>
<td>None to mild</td>
<td>None to mild</td>
<td>+/-</td>
<td>+/++</td>
</tr>
<tr>
<td><strong>Schirmer score mm/5 min</strong></td>
<td>Variable</td>
<td>≤ 10</td>
<td>≤ 5</td>
<td>≤ 2</td>
</tr>
</tbody>
</table>

**Symptoms: scratching, fogging and redness**

Discomfort upon the use of ophthalmic drops with BAK as a preservative influences the action of an active antiglaucoma drug substance and reduces the patient’s compliance in regular application with ophthalmic therapy (14). The treatment of dry eye symptoms primarily consists of long-term use of different artificial tears available on the market, but this is not always enough to achieve an optimal effect (15).

Hylo®gel is lubricating eye drops for the special requirements of chronically dry eyes and particularly severe cases. They contain hyaluronic acid in the concentration of 0.2%, which forms an optimal viscosity of the tear layer on the corneal surface, without blurring vision, and supports the regeneration of the eye surface; the drops are free from preservatives and phosphates, and are packed in the patented multi-dose device that prevents the contamination of its contents. Starting with Bioptron light therapy, using the Bioptron lamp (Figure 1), Bioptron-AG, Swiss company, power of 100-240 V-T2A, we achieve a natural, medical method that boosts regenerative capacity and a favorable response to healing (16). Bioptron light therapy is efficient in the elimination of allergic reactions, signs and symptoms of dry eye, as a result of topically applied antiglaucoma therapy with Benzalkonium-chloride as a preservative.

Figure 1. Bioptron®lamp

Bioptron light therapy makes balance within metabo-
lism, improving capillary circulation, immunity stimulation, relieving pain and establishing balance of tissue electromagnetic field (17). Through the eye, visible and infrared light come to the brain, influencing the function and balance of endocrine gland secretion (18). Bioptron biophysical effects depend on the polarized wave energy and polarized wave length. Polarized waves are of the same frequency but they are incoherent, the light intensity at the target tissue is constant, without variation in energy. Energy is very low, 1 - 2.4 J/cm without thermal effects, energy density is 40mW. Bioptron light is polychrome, wave frequency is from 400 nm (including blue, visible radiation) up to 2000 nm (representing infrared waves). Ultraviolet, chemically active radiation is completely eliminated with a special filter (19). Polarized beam penetrates into tissue up to 2.5 cm deep, depending on the exposure time. It stimulates fibroblast and collagen fiber production with no side effects. During and after the treatment, Bioptron light therapy activates immunity, both local and systemic. Being completely safe for eyes, even in pregnant women, the therapy contributes to the fight against viruses (20). The aim of this study was to determine the effectiveness of Bioptron light therapy in the elimination of symptoms and signs of discomfort on the anterior eye surface in patients with topical antiglaucoma therapy with preservative BAK, in whom therapy with Hydrogel solution is not enough to eliminate the symptoms and signs of dry eye.

Methods

From May 2014 up to January 2016, a sample of 36 middle-aged patients (72 eyes) was examined, 19 women and 17 men, from the age of 52 to 68. All of them had dry eye symptoms, ranging from mild/normal to moderate and severe. They were all treated longer than one year, with the same topical antiglaucoma drugs, Cosopt®2% (dorsolamide-hydrochloride 20mg /ml and timolol-maleate 5mg/ml), twice a day, which contain the preservative BAK in a concentration ≤ 0.01%. Patients underwent complete internal examination for the purpose of excluding any other systemic disease which may cause dry eye syndrome and reduce regenerative capacity of mucous membranes and the skin (21). We did complete ophthalmic examination for the purpose of excluding any other disease, injuries and previous surgical treatment of eyes. All patients with diagnosis of chronic blepharitis, meibomitis or any other eye infection were excluded from the study as those diseases may also lead to dry eye due to a deficit in lipid outer layer, and consequently, to evaporative dry eye (22). We examined the symptoms like scratching, fogging and redness of the eyes. Patients were divided in the same three groups, with different topical treatment that followed for the next four weeks. During the four weeks, the first and second group were on different topical therapy, and the third, control group, was treated only with Cosopt® twice a day. The first group of 12 middle-aged patients (24 eyes), 6 women and 6 men, was treated with Cosopt and topical solution Hydrogel three times a day. The second group of 12 middle-aged patients (24 eyes), 6 women and 6 men, was treated with Cosopt®, Hydrogel three times a day, and Bioptron light therapy, three days a week. Patients were sitting in a comfortable chair, with their eyes closed, with previously cleaned eyelids, occasionally blinking. Bioptron lamp was lined at an angle of 90°, at a distance from 5 cm to 10 cm, exposure time was 5 min. The third, control group, involved 12 middle-aged patients (24 eyes), 7 women and 5 men, on Cosopt® therapy.

Parameters of better drug tolerability were criteria set by “Dry eye severity grading scheme” (23). As an objective parameter, Shirmer’s test 1 was done in all patients, after putting in 0.5% tetracaine solution two times during five minutes for the purpose of measurement of the basal tear secretion, and elimination of the reflex tear secretion (Table 2). Measurement of basal tear secretion was done two minutes after the last use of 0.5% tetracaine drops (24). We used Alcon Laboratories Shirmer’s tear test sterile strips, 35 mm in length, in the fornix of the lower eyelid at the junction of the middle and outer third, for 5 min with eyes closed. Humidity of strips was measured in mm, with a ruler. Finding the pieces of paper with humidity less than 10 mm was taken as a pathological value. During the treatment, patients were not on any other systemic therapy (25). The results processing was done using statistical Student’s X² test and Student’s T-test.

Table 2. Previous measurement

<table>
<thead>
<tr>
<th>Mild/normal symptoms</th>
<th>Moderate symptoms</th>
<th>Severe symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>First group</td>
<td>4 eyes (5.56%)</td>
<td>6 eyes (8.33%)</td>
</tr>
<tr>
<td>Second group</td>
<td>4 eyes (5.56%)</td>
<td>6 eyes (8.33%)</td>
</tr>
<tr>
<td>Third control group</td>
<td>4 eyes (5.56%)</td>
<td>6 eyes (8.33%)</td>
</tr>
</tbody>
</table>

First group: 6 women and 6 men (24 eyes), treated with Cosopt® and Hydrogel
Second group: 6 women and 6 men, (24 eyes), treated only with Cosopt®, Hydrogel and Bioptron® light therapy
Third control group: 7 women and 5 men, (24 eyes), treated only with Cosopt®
Results

Symptoms: cratching, fogging and redness of the eyes

In previous measurement, before starting the therapy, mild/normal symptoms appeared in two patients (4 eyes 5.56%) in each of the three groups, moderate symptoms appeared in 3 patients, (6 eyes, 8.33%) in each of the groups, and severe symptoms appeared in 7 patients (14 eyes, 19.44%) in each of the three groups (Table 2). They were divided into the same three groups according to symptoms. Age and gender were not statistically different.

Table 3. Previous measurement: Shirmer’s test 1

<table>
<thead>
<tr>
<th>Shirmer’s test 1</th>
<th>&gt; 10 mm mild/normal</th>
<th>≤ 10 mm moderate</th>
<th>≤ 5mm sever</th>
</tr>
</thead>
<tbody>
<tr>
<td>First group</td>
<td>6 eyes (8.33%)</td>
<td>6 eyes (8.33 %)</td>
<td>12 eyes (16.67%)</td>
</tr>
<tr>
<td>Second group</td>
<td>2 eyes (2.78%)</td>
<td>10 eyes (13.89%)</td>
<td>12 eyes (16.67%)</td>
</tr>
<tr>
<td>Third control group</td>
<td>2 eyes (2.78%)</td>
<td>6 eyes (8.33%)</td>
<td>16 eyes (22.22%)</td>
</tr>
</tbody>
</table>

First group: 6 women and 6 men (24 eyes) treated with Cosopt®and Hylo®gel
Second group: 6 women and 6 men (24 eyes) treated only with Cosopt®, Hylo®gel and Bioptron®light therapy
Third control group: 7 women and 5 men (24 eyes) treated only with Cosopt®

Shirmer’s test 1: basal tear secretion

In all three groups, 36 patients (72 eyes) in total, in the majority of patients severe decrease in the basal tear secretion (55.56%) was reported, moderate symptoms were found in 30.56% of participants, and mild/normal symptoms were reported in 13.89% of participants.

Symptoms: scratching, fogging and redness of the eyes

After 4 weeks of different treatment of

Table 4. Results after treatment

<table>
<thead>
<tr>
<th>Mild/normal symptoms</th>
<th>Moderate symptoms</th>
<th>Severe symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>First group</td>
<td>14 eyes (19.44%)</td>
<td>6 eyes (8.33%)</td>
</tr>
<tr>
<td>Second group</td>
<td>20 eyes (27.78%)</td>
<td>4 eyes (5.56%)</td>
</tr>
<tr>
<td>Third, control group</td>
<td>4 eyes (5.56%)</td>
<td>6 eyes (8.33%)</td>
</tr>
</tbody>
</table>

First group: 6 women and 6 men (24 eyes) treated with Cosopt®and Sol.Hylo®gel
Second group: 6 women and 6 men (24 eyes) treated with Cosopt®, Sol.Hylo®gel and Bioptron®light therapy
Third control group: 7 women and 5 men (24 eyes) treated only with Cosopt®

Table 5. Results after treatment: Shirmer’s I test

<table>
<thead>
<tr>
<th>Shirmer’s test 1</th>
<th>&gt; 10 mm mild/normal</th>
<th>≤ 10 mm moderate</th>
<th>≤ 5mm sever</th>
</tr>
</thead>
<tbody>
<tr>
<td>First group</td>
<td>8 eyes (11.11%)</td>
<td>6 eyes (8.33%)</td>
<td>10 eyes (13.89%)</td>
</tr>
<tr>
<td>Second group</td>
<td>14 eyes (19.44%)</td>
<td>8 eyes (11.11%)</td>
<td>2 eyes (2.78%)</td>
</tr>
<tr>
<td>Third control group</td>
<td>2 eyes (2.78%)</td>
<td>2 eyes (2.78%)</td>
<td>20 eyes (27.78%)</td>
</tr>
</tbody>
</table>

First group: 6 women and 6 men (24 eyes) treated with Cosopt®and Sol.Hylo®gel
Second group: 6 women and 6 men (24 eyes) treated with Cosopt®, Sol.Hylo®gel and Bioptron®light therapy
Third control group: 7 women and 5 men (24 eyes) treated only with Cosopt®
**Shirmer’s test 1: basal tear secretion**

After the treatment, statistically significant improvement in severe deficit in tear secretion was found in 2 eyes (2.78%) in Group 1. Statistically significant improvement in severe deficit was found in 2 eyes (2.78%), whereas moderate deficit in tear secretion was observed in 2 eyes (2.78%) in group 2 patients. In third, control group, there was a decrease in tear secretion, and moderate deficit in 4 eyes turned into severe tear deficit. The role of Bioptron light therapy (p < 0.001) is evident especially in severe and moderate symptoms and signs.

**Discussion**

In Group 1 and Group 2 patients, part of therapy was Hylo®gel solution, one of the best choices for the treatment of dry eye in our country. This sterile solution without any preservatives, successfully relieved symptoms of dry eye in 2-4 weeks. It was our choice in therapy, because it is widely applied in our country and well tolerated by patients. Topically applied Hylo®gel may help in the elimination of some symptoms, but it is not enough without Bioptron® light therapy. Because of dry eye, on a cellular level, discrete inflammatory changes appear, secretion of tears is decreased, corneal epithelium becomes thinner as a result of decreasing of corneal sub-basal nerve density. Treatment by Bioptron light therapy increases tissue anti-inflammatory cytokines and contributes to the regeneration of corneal nerves. Bioptron® light therapy reaches its full efficiency as addition to Hylo®gel therapy and by using both of them healing of severe cases of keratoconjunctivitis sicca can be achieved, as was confirmed in our research. With ageing, corneal epithelium becomes thinner and precorneal tear film becomes more and more unstable (26). In dry eye, which is a consequence of other systemic disorders and therapy, patients have healthy corneal endothelium and basement-membrane, however, after therapy with BAK as a preservative, we found cytotoxic effects, higher endothelium damage, epithelium edema, bullous keratopathy, and higher incidence of eye inflammation (27).

Therapeutic potential of the Bioptron® light in the treatment and healing of wounds has been proven. There are no adverse reactions during and after this non-invasive therapy. Antimicrobial preventive effect, antidepressant effect and many other fields of application present additional benefits to each patient (28). It is necessary to attend a short course to apply Bioptron lamp. Low-power laser treatment has a stimulatory effect on wound healing, Bioptron light is also low-power light source, but differs from it as it is polychromatic rather than monochromatic (29).

**Conclusion**

We proved that Bioptron light therapy is successful and effective in disappearance of symptoms and signs of dry eye as a consequence of long-lasting antiglaucoma therapy with BAK as a preservative. Bioptron light therapy is non-invasive, easily applicable, without any contraindications. Bioptron lamp is portable, suitable for home use and for immobile patients. Patients are very satisfied with the introduction of Bioptron light therapy in care of dry eye symptoms, so comfort and compliance of patients have been improved. Bioptron lamp is recommended for additional therapy for all antiglaucoma patients.
References

BIOPTRON SVETLOSNA TERAPIJA SUVOG OKA USLED DUGOTRAJNE TOPIKALNE ANTIGLAUKOMNE TERAPIJE BENZALKONIUM-CHLORIDOM

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Benzalkonium-chloride je najčešće korišćeni konzervans u savremenoj antiglaukomnoj topikalnoj terapiji, sa mnogobrojnim prednostima i kumulativnim neželjenim dejstvima na prednju površinu oka. Benzalkonium-chloride je klasifikovan kao težak iritans mukoznih membrana, što rezultira suvoćom prednjeg očnog segmenta.

Cilj našeg rada bio je naučna potvrda efikasnosti Bioptron svetlosne terapije u indukciji povoljnih reakcija na ozdravljenje, otklanjanju simptoma, znakova suvog oka kao posledicu dugotrajne topikalno primenjene antiglaukomatozne terapije Benzalkonijum-chloridom kao konzervansom.

Izvršeno je ispitivanje na 36 bolesnika (72 oka) koji su bili podeljeni u tri grupe: prva i druga grupa sa različitim pristupom u terapiji suve prednje površine oka i treća, kontrolna grupa. Kompletan oftalmološki pregled bolesnika urađen je pre početka ispitivanja i posle završene svetlosne terapije Bioptronom. Pregled je obavljen prema kriterijumima “Dry eye severity grading scheme”, a kao objektivan parametar rađen je Shirmerov I-test. U drugoj grupi bolesnika, lečenih Hylo®gel kapima i Bioptron svetlosnom terapijom, simptomi i znaci su statistički značajno redukovani sa 27,78% na 5,56% (p < 0,001).

Vrednosti Širmerog I-testa pokažu poboljšanje sa 30,56% na 13,89% deficit a sekreciji suza (p < 0,001). Simptomi i znaci suvoće prednje površine oka su statistički značajno redukovani. Tolerancija antiglaukomne terapije, komfor i komplijansa bolesnika su značajno poboljšani. Neophodno je uključiti Bioptron svetlosnu terapiju kod svih bolesnika na antiglaukomnoj terapiji Benzalkonijum-chloridom kao konzervansom.

Ključne reči: Benzalkonum-chloride, Keratoconjunctivitis sicca, terapija Bioptron® lampom