Comparative Study between the Effect of Dorzolamide/Timolol Fixed Combination and Brimonidine/Timolol Fixed Combination on Corneal Endothelium

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Abstract

Background: Glaucoma is one of the most important cause of irreversible blindness in the world. Elevated Intraocular Pressure (IOP) remains the main known risk factor for the development and progression of the disease. The main therapeutic goal is to preserve visual function by reducing the IOP, which is the key modifiable risk factor.

Aim of Study: Is to compare the effect and safety of Dorzolamide/Timolol-Fixed Combination (DTFC) and Brimonidine/Timolol-Fixed Combination (BTFC), on corneal endothelium after 3 months.

Patient and Methods: This comparative non-randomized controlled clinical trial study included 57 eyes of 57 patients which was conducted in Damietta Eye Hospital. Their age ranged from 20-70 years old. The study population was divided into two groups: First group receiving DTFC: Included 27 eyes of 27 patients with open angle glaucoma and second group receiving BTFC included 30 eyes of 30 patients with open angle glaucoma.

Result: Show that this adjusted difference between group 1 and group 2 through 3 months follow-up had no statistical significance in all variables such as IOP (p=0.172), CCT (p=0.072) and CD (p=0.406).

Conclusion: The patients that received two fixed-combination (dorzolamide/timolol) and (brimonidine/timolol) had no statistically significant effect on CCT and ECD after 3 months from using these drugs.

Key Words: Dorzolamide – Brimonidine – Combination – Glaucoma – Cornea – Endothelium.

Introduction

GLAUCOMA is among the leading causes of blindness and a major health problem in the developed world. Elevated Intraocular Pressure (IOP) is the most important known risk factor for the progression of visual field loss in patients with glaucoma. Despite that the substantial specular microscopy can provide a noninvasive morphologic analysis of the corneal endothelial cell layer, it can also provide a measure of the endothelial cell physiologic reserve from aging, ocular surgical procedures, pharmaceutical exposure, and general health of the corneal endothelium [1].

We need to detect corneal endothelial cell affection after treatment with fixed-combinations of glaucoma medication (dorzolamide/timolol) and (brimonidine/timolol) after 3 months.

IOP lowering effect possible with monotherapy, many patients may need to use two or more medications to reach a target IOP sufficiently low to halt further visual deterioration [2].

When multiple medications are required, the use of a fixed combination of two IOP-lowering medications offers several advantages over the concomitant use of the individual components. In addition to the convenience of a single bottle, which may improve patient compliance, fixed combinations of IOP-lowering medications also reduce the likelihood of drug dilution caused by the instillation of multiple eye drops, minimize ocular exposure to preservatives, and may lead to a decrease in costs and patient copayments for the medications [3]. Then in this study the effect and safety of fixed-combinations on corneal enthelium will be compared.

Measurement of corneal endothelial cell density is important both for clinical diagnosis as well as clinical studies. Since endothelial cell loss is considered irreversible in humans, even small changes in endothelial cell density are relevant [4]. Endothe-
Specular microscopy of the corneal endothelial cell layer is an important diagnostic tool in clinical practice. It is not only used to assess the health of the endothelium in patients with corneal diseases, but is also part of the routine examinations after corneal transplantation. In addition to its clinical use, follow-up endothelial cell measurements are used in clinical trials to assess the corneal safety of surgical techniques or new materials [4].

Fixed combinations of glaucoma medications, in most cases, provide similar IOP reduction to that observed with simultaneous administration of their individual components, simplify adjunctive medication regimens, reduce the incidence of adverse events, and may improve adherence and long-term tolerability [5].

Fixed-combination brimonidine-timolol provided the same or greater IOP lowering compared with fixed-combination dorzolamide-timolol [6]. Irreversible corneal decompensation was encountered in patients treated with topical dorzolamide [7]. This study is aiming to detect the effect of brimonidine also on corneal endothelium.

A more detailed comparison of the effect of two combinations on corneal endothelium can be made by recording CCT and measure IOP after a 3 months period.

**Patients and Methods**

**Patients:**

This comparative non-randomized controlled clinical trial study included 57 eyes of 57 patients of open angle glaucoma which was conducted in Damietta Eye Hospital during the period from June 2018 to May 2019. Their age ranged from 20-70 years old. The study population was divided into two groups:

- First group receiving dorzolamide/timolol fixed-combination: Included 27 eyes of 27 patients with open angle glaucoma.
- Second group receiving brimonidine/timolol fixed-combination: Included 30 eyes of 30 patients with open angle glaucoma.

**Exclusion criteria:**

- Age more than 70 years, or less than 20 years.
- Fuchs’ Endothelial Dystrophy.
- Closed-angle glaucoma.
- History of ophthalmic disease other than glaucoma.
- Sever dry eye.
- Corneal opacity.
- Any known contraindication to beta-blockers, alpha-agonists, or carbonic anhydrase inhibitors including clinically significant heart disease, second or third degree heart block or sinus bradycardia and others.
- Previous sensitivity or allergic reaction to brimonidine or dorzolamide.

The corresponding consent form followed the tenets of the Declaration of Helsinki. A written informed consent was obtained from each participant before enrollment. All applicable institutional regulations concerning the ethical use of human volunteers were followed during this research.

**Methods:**

All cases underwent a complete ophthalmic examination, medical and family history.

**Examination included:**

- Non-cycloplegic refraction was determined using an autorefractometer (RM-8900)(Topcon, Japan).
- Anterior segment examination using slit lamp.
- Gonioscopy was done using (Gold man three-mirror gonioscopic lens).
- Applanation tonometry used to measure IOP as the patient was seated comfortably at the slit lamp.
- (SP-1P, specular microscopy) used central method. Patients were instructed to fixate on the intrinsic fixation target during the whole process of specular microscope examination. Auto-focusing and manual cell selection was applied in the examination. Images with good quality were chosen for measurement of parameters. The eight parameters of endothelium layer were analyzed by the built-in software, including Enendothelial Cell Density (ECD), percent Hexagonality (HG%), Coefficient of Variability (CV), Central Corneal Thickness (CCT), size of minimal cell (Smin), size of maximal cell (Smax), average cells size (Savg), size standard deviation (Ssd). The image with the analyzed data was then printed out. These scans were performed by single experienced doctor.
- These examinations were done for each group first at base line (Gonioscopy-IOP-specular microscopy) and then repeated after 3 months (IOP-specular microscopy) started at June 2018.
Data management & statistical analysis:
- The data collected was revised, coded, tabulated and introduced to a PC using statistical package for social sciences (IBM SPSS 20.0). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

I- Descriptive statistics: Mean, Standard Deviation (+ SD) and range for parametric numerical data, while median and Interquartile Range (IQR) for non parametric data.

II- Analytical statistics: Independent sample t-test was used to assess the statistical significance of the difference of a parametric variable between two independent means of two study groups. Paired sample t-test was used to assess the statistical significance of the difference of a parametric variable between two means of one study group before and after intervention.

Results

This study included 57 eyes of 57 patients, one eye from each patient. They were divided into two groups. Group 1 (dorzolamide/timolol) included 27 patients and group 2 (brimonidine/timolol) included 30 patients. The mean baseline Intraocular Pressure (IOP) was (20±4.31mmHg) and (18.50±4.16mmHg) in the patients treated with dorzolamide/timolol and brimonidine/timolol, respectively (p=0.187) (no statistical difference).

The mean baseline of Central Corneal Thickness (CCT) was (509.22±33.71mm) and (512.52±25.96 mm) in group 1 and group 2, respectively (p=0.676) (no statistical difference).

The mean baseline of Endothelial Cell Density (ECD) was (2578.15±418.59 cells/mm²) and (2577.07±328.59 cells/mm²) in group 1 and 2, respectively (p=0.546) presented in (Table 2). This results shows that there was no statistically significant difference between group 1 and group 2 after 3 months presented in (Table 2).

Also, there were no significant changes in all of the studied variables after 3 months as compared to baseline in Group I (Dorzolamide + Timolol). In our study mean CCT at baseline was 509.22±33.71mm and after 3 months was 508.81±33.44 mm (p=0.827). Also, there were decreased in ECD after 3 months but not significant. ECD at baseline in patients treated with dorzolamide/timolol was 2578.15±418.59 cells/mm² and after 3 months was 2443.44±349.33 cells/mm² (p=0.058) presented in (Table 3).

Also, there were no significant changes in all of the studied variables after 3 months as compared to baseline in Group 2 (brimonidine/timolol). CCT at baseline in patients treated with was 512.52±25.96 and after 3 months was 512.47±27.36mm (p=0.863). There were decreased in ECD after 3 months but not significant). ECD at baseline was 2577.07±328.59 cells/mm² and after 3 months was 2627.48±293.04 cells/mm² (p=0.546) presented in (Table 4).

The results show that this adjusted difference between group 1 and group 2 as regard baseline variables such as IOP, CCT and CD presented in (Table 1).

The mean IOP after 3 months were (18.67±3.55 mmHg) in group 1 and (18.97±4.00 mmHg) in group 2 (p=0.767) presented in (Table 2). The mean CCT after 3 months were (508.81±33.44 mm) and (512.47±27.36mm), in group 1 and group 2, respectively (p=0.652) presented in (Table 2).

The mean ECD after 3 months were (2443.44±349.33 cells/mm²) and (2577.07±328.59 cells/mm²) in group 1 and 2, respectively (p=0.143) presented in (Table 2). This results shows that there was no statistically significant difference between group 1 and group 2 after 3 months presented in (Table 2).

Table (1): Comparison between Group I (Dorzolamide + Timolol) & Group II (Brimonidine + Timolol) as regard baseline variables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 Dorzolamide + Timolol</th>
<th>Group 2 Brimonidine + Timolol</th>
<th>Independent sample t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP (mmHg)</td>
<td>20.00 ± 4.31</td>
<td>18.50 ± 4.16</td>
<td>-0.525</td>
<td>0.602</td>
</tr>
<tr>
<td>CCT (µm)</td>
<td>509.22 ± 33.71</td>
<td>512.52 ± 25.96</td>
<td>-0.420</td>
<td>0.767</td>
</tr>
<tr>
<td>CD (cells/mm²)</td>
<td>2578.15 ± 418.59</td>
<td>2627.48 ± 293.04</td>
<td>-0.525</td>
<td>0.406</td>
</tr>
</tbody>
</table>

CCT: Central Corneal Thickness.
CD: Cell Density.
IOP: Intraocular Pressure.
### Table (2): Comparison between Group I (Dorzolamide + Timolol) & Group II (Brimonidine + Timolol) as regard all studied variables after 3 months.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Independent sample t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>± SD</td>
</tr>
<tr>
<td>IOP (mmHg)</td>
<td>18.67</td>
<td>3.55</td>
<td>18.97</td>
<td>4.00</td>
</tr>
<tr>
<td>CCT (µm)</td>
<td>508.81</td>
<td>33.44</td>
<td>512.47</td>
<td>27.36</td>
</tr>
<tr>
<td>CD (cells/mm²)</td>
<td>2443.44</td>
<td>349.33</td>
<td>2577.07</td>
<td>328.59</td>
</tr>
</tbody>
</table>

### Table (3): Changes occurred in all of the studied variables after 3 months as compared to baseline in Group I (Dorzolamide + Timolol).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Timing</th>
<th>Paired t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 3 months</td>
<td>Mean</td>
</tr>
<tr>
<td>CCT (µm)</td>
<td>509.22</td>
<td>508.81</td>
<td>33.71</td>
</tr>
<tr>
<td>CD (cells/mm²)</td>
<td>2578.15</td>
<td>2443.44</td>
<td>418.59</td>
</tr>
</tbody>
</table>

### Table (4): Changes occurred in all of the studied variables after 3 months as compared to baseline in Group II (Brimonidine + Timolol).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Timing</th>
<th>Paired t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 3 months</td>
<td>Mean</td>
</tr>
<tr>
<td>CCT (µm)</td>
<td>512.22</td>
<td>512.47</td>
<td>25.96</td>
</tr>
<tr>
<td>CD (cells/mm²)</td>
<td>2627.48</td>
<td>2577.07</td>
<td>293.04</td>
</tr>
</tbody>
</table>

### Table (5): Comparison between Group I (Dorzolamide + Timolol) & Group II (Brimonidine + Timolol) as regard mean difference of variables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Independent sample t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>± SD</td>
<td>Mean</td>
<td>± SD</td>
</tr>
<tr>
<td>IOP (mmHg)</td>
<td>-1.33</td>
<td>4.62</td>
<td>0.47</td>
<td>3.69</td>
</tr>
<tr>
<td>CCT (µm)</td>
<td>-0.41</td>
<td>9.62</td>
<td>-4.50</td>
<td>10.16</td>
</tr>
<tr>
<td>CD (cells/mm²)</td>
<td>-211.26</td>
<td>221.30</td>
<td>-161.73</td>
<td>159.51</td>
</tr>
</tbody>
</table>

### Discussion

Evaluation of corneal endothelium is very important in a glaucomatous patient receiving antiglaucoma treatment. The mechanisms leading to lowering of the cell counts in patients with glaucoma are not clear. Gango et al. formulated three hypotheses: (A) Damage from direct compression of the corneal endothelium due to higher intraocular pressure, (B) Congenital alteration of both the corneal endothelial cell layer and the trabecular meshwork in patients with glaucoma and (C) Glaucoma medication toxicity [8].

In our patients, topical carbonic anhydrase inhibitor/beta-blocker combination and alpha-agonist/beta-blocker combination were used. No significant complications were found regarding topical treatment. No significant changes were observed in corneal thickness or in endothelial cell density in our patients who were examined after treatment with dorzolamide/timolol and brimonidine/timolol as, these results could be explained by the short period of 3 months of the study.

Many studies have been conducted to evaluate the effect of different antiglaucoma topical medication on CCT and ECD in adult patients in agreement with our result in the study of Lass et al. Timolol, betaxolol, and dorzolamide were found to be equivalent in terms of corneal endothelial cell loss and corneal thickness after 1 year of therapy in 298 adult subjects with ocular hypertension and open-angle glaucoma with previously normal corneas. All 3 treatments exhibit good long-term corneal tolerability in patients with normal corneas at baseline [9].

Korey et al., found no significant difference in ECD and CCT between patients with normal IOP, with untreated OH, with treated OH, and with primary open-angle glaucoma [10].

Kaminiski et al., reported that patients treated with 2% dorzolamide mean corneal thickness was slightly increased on day 1 and returned to baseline measurements at the following visits and endothelial cell count showed no change [11].
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Giasson et al., tried to investigate whether dorzolamide alters corneal hydration control in patients with glaucoma or ocular hypertension. They did not observe significant changes in corneal thickness or in endothelial cell density in the small sample of patients who were examined. They concluded that in patients with glaucoma or ocular hypertension with normal endothelium and without baseline corneal edema, inhibition of carbonic anhydrase with dorzolamide does not seem to affect corneal hydration control [12].

The results of many studies suggest that dorzolamide and preservative-free dorzolamide are not significantly toxic to corneal endothelium under usual ocular conditions [13].

In other studies by Wierzbowska et al., observed that CCT was nearly stable in eyes treated with different type of topical antiglaucoma drugs either in monotherapy or combined therapy [14].

Topical carbonic anhydrase inhibitors reduce the corneal pumping function, resulting in increased corneal water content and corneal thickness. However, this side effect appeared only in patients with compromised corneas and a previous history of corneal pathology [11].

It is in agreement with our results: ECD and CCT values in eyes treated with dorzolamide/timolol were similar to values of ECD and CCT in eyes treated with brimonidine/timolol. No significant changes of CCT and ECD after 3 months of treatment for two fixed-combinations (dorzolamide/timolol and brimonidine/timolol) were found.

However, in disagreement with our results Bourne and McLaren observed that among the available topical drugs, only dorzolamide seems to have a possible negative effect on the corneal endothelium [15].

Viswanathan et al., also reported that CCT fell significantly in 187 eyes treated with topical antiglaucoma medications for at least 3 years: Mean CCT reduction was 12.29 µm [16].

Gangon observed that those subjects receiving three or four glaucoma medications had lower cell counts than those receiving one or two medications [17].

Benzalkonium chloride (BAK) is the most popular preservative and it is considered to have harmful effect on the ocular surface. It is known that BAK is also toxic for corneal endothelial cells and several clinical cases have proved this fact [18].

Lee et al., showed that long-term treatment with BAK containing anti-glaucoma medication appears to be the main contributor to corneal toxicity.

Ayaki et al., evaluated the toxicity of antiglaucoma medications to corneal endothelial cells using an in vitro toxicity assay and they observed that it depends on the presence of BAK. They concluded that corneal endothelium damage due to antiglaucoma eye drops may occur only in rare cases [13].

Based on the existing data, it seems rational to support the use of benzalkonium-free solutions whenever possible, especially in young patients who expected to need multiple and prolonged topical treatments.

In conclusion, our study confirmed that the patients receiving two fixed-combinations (dorzolamide/timolol and brimonidine/timolol) did not affect CCT and ECD after 3 months of treatment. Although the decrease in CD in group I were higher than in group 2 as (p=0.058) and (p=0.546), respectively but still remain not statistically significant. There were no statistically significant differences between ECD and CCT of eyes treated with different kinds of topical antiglaucoma medications such as (dorzolamide/timolol and brimonidine/timolol).

For better evaluation the effect of DTFC & BTFC on corneal endothelium, longer period and larger sample is recommended.

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دراسة للمقارنة بين تأثير المركب الدوائي دورزولاميد/تيومولول

بـ:بريمونيدين/تيومولول على بطانة القرنية

المقدمة: تعتبر المياه الزرقاء من بين الأساسات الرئيسية للعيان ومشكلة صحية كبيرة في العالم المتقدم. ضغط العين المرتفع عامل خطير

لقد كان المجال البصري في المرضى الذين يعانون من المياه الزرقاء على الرغم من إنخفاض الضغط مع العلاج الأحادي، قد يحتاج العديد من المرضى إلى استخدام مركبين من الأدوية أو أكثر للوصول إلى المستوى المستهدف من الضغط لتفادي تدهور البصر.

قياس كفاءة الخلايا البطانية القرنية مهما للتشخيص والدراسات الإكلينيكية. ويعتبر الفحص المجهرى يمكن أن يؤثر بصورة موثوقياً

لتطوير الخلايا البطانية القرنية. كما يمكن أن يساعد التغيير النشط للخلايا البطانية الناجم عن الشيخوخة والإجراءات الجراحية للعين، والتعرض للأدوية والمسببات الأخرى للضعف في الخلايا البطانية القرنية.

طريقة البحث: تم فحص 57 عين لـ 27 شخص عين واحدة من كل شخص لديه مرض جلوكوما مفتوح الزاوية العينية. وتم تقسيمهم إلى مجموعتين: الأولى 27 شخصًا وثانيهما 30 شخصًا. وبعد إعطاء المرضى فحص عين شامل مسار العين، تم إعطاء المجموعة الأولى المركب الدوائي دورزولاميد/تيومولول والمجموعة الثانية المركب الدوائي بريمونيدين/تيومولول لمدة 3 أشهر ومتابة تأثيرهم على الخلايا البطانية القرنية باستخدام المفسح المجهرى.

نتائج البحث: وجد أن هذه الأدوية لا تؤثر سلبياً بدرجة ذات قيمة إحصائية على الخلايا البطانية القرنية بعد الاستخدام لمدة 3 أشهر بالرغم من تأثيرها الطفيف ولكن ليس ذات قيمة إحصائية.