A STUDY OF THE EFFECTS OF TOPICAL TIMOLOL 0.5% AND BIMATOPROST 0.03% ON THE OCULAR SURFACE

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ABSTRACT

BACKGROUND

Antiglaucoma medications have increased in number and use over the past two decades. Timolol and bimatoprost are used as first line therapy in many centres. Adverse effects on the ocular surface have been noted with many topical medications. The aim of the study is to study the effects of timolol and bimatoprost on the ocular surface.

MATERIALS AND METHODS

Newly-diagnosed patients with POAG were randomly allocated to receive timolol or bimatoprost. Conjunctival impression cytology, tear film break-up time, Schirmer’s and rose bengal score were done at baseline, one, three and six months.

RESULTS

The tear film break-up time reduced in both groups over the study period with the reduction in the timolol group of 7.3 seconds being more pronounced and statistically significant. The mean reduction in Schirmer test values was greater in the timolol group (9.1 mm) at both 3 months and 6 months and was statistically significant. The rose bengal scores over the period of six months in both groups were being statistically significant at three and six months in the timolol group, while rise in scores was seen only at six months in the bimatoprost group. Conjunctival impression cytology was carried out at baseline and six months. Statistically, significant cytological changes were seen only in the timolol group after six months of therapy.

CONCLUSION

The adverse effects on ocular surface were more pronounced with timolol when compared with bimatoprost.

KEYWORDS

Ocular Surface Disease, Timolol 0.5%, Bimatoprost 0.03%.

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BACKGROUND

Ocular surface disease occurs when there is a disruption in the cellular functional and morphological integrity of the ocular surface. It is seen when there is widespread disruption of the normal homeostasis of the ocular surface, which may occur because of decreased tear production, excessive tear evaporation or an abnormality in the mucin or lipid components of the tear film. It is accompanied by increased tear film osmolarity and inflammation of the ocular surface. Ocular surface diseases have been reported with several topical and systemic medications. Examples of topical medications include antiglaucoma drugs, topical anaesthetic agents, while systemic medications include diuretics, amiodarone and isoretinoin. Among the topical medications, which cause ocular surface changes, antiglaucoma medications have become increasingly important. This is in part due to the increasing number of antiglaucoma medications available, in part due to the increasing burden of disease and in part due to the earlier detection of disease.

Primary open angle glaucoma is the second most common cause of blindness all over the world. Medical management is the treatment of choice and surgery is usually reserved for cases that cannot be controlled with drugs.

Glaucoma therapy is lifelong and topical agents used over long time are likely to cause changes in ocular surface particularly reduction in tear secretion, changes in tear film break-up time and changes in the conjunctival epithelium.

Kamath et al in their study found at the end of six months reduced goblet cell density in six patients (28%) from timolol group and two patients (9%) in the latanoprost group. The correlation found that the decrease in goblet cell density was seen in conjunctival impression cytology specimens of
patients with decrease in Schirmer's and TFBUT values, which explains the reason for changes in these values.

Beta-adrenergic blocking agents have remained the mainstay in management of glaucoma for the past 20 years in spite of newer drugs being introduced such as prostaglandin analogues, carbonic anhydrase inhibitors and alpha-adrenergic agonists. Both timolol 0.5% and bimatoprost 0.03% are effective in adequately controlling intraocular pressure when used as monotherapy with timolol being more cheaper and readily available while bimatoprost is more efficacious. This study therefore aims to compare the effects of two commonly used antiglaucoma drugs, timolol 0.5% and bimatoprost 0.03% on the ocular surface.

MATERIALS AND METHODS
Newly-diagnosed subjects of glaucoma/ocular hypertension who were started on monotherapy/either timolol 0.5% or bimatoprost 0.03% were included in the study. The study subjects were allocated randomly into two groups. Group I comprising those who received timolol 0.5% and group II those who received bimatoprost 0.03%.

All patients underwent a baseline evaluation, which included medical and ophthalmic history. The subjects were asked relevant history and dry eye symptoms graded. A complete anterior segment evaluation was done followed by Tear Film Break-Up Time (TFBUT), Schirmer test I, rose bengal test and Conjunctival Impression Cytology (CIC). A tear film BUT of less than 10 seconds was taken as abnormal. Schirmer normal values range between 10 to 30 mm in 5 minutes. Values of 5 to 10 mm are suggestive of mild-to-moderate dry eye and less than 5 mm are suggestive of severe dry eye. The rose bengal score is a quantified version of the original rose bengal test. The intensity of staining of both the medial and lateral bulbar conjunctiva and the cornea was scored, each section up to three points (1- Sparsely scattered, 2- Densely scattered, 3 - Confluent). A score of 4 or more was considered significant.

CIC was done with Periodic Acid-Schiff and Papanicolaou stain following the standard procedure. All slides were examined and staged according to the staging of Natadasstra et al. After the initial baseline evaluation, the follow up evaluations were done at 1 month, 3 months and 6 months. Conjunctival impression cytology was done at baseline and at the end of six months. All data including demographic information, clinical examination and both qualitative and quantitative data were entered into a database software programme. Nominal categorical variables were analysed using Chi-square test. Within group, changes from baseline were analysed using the Mann-Whitney test. Continuous variables were analysed using ANOVA with within group changes from baseline analysed using paired t-test.

RESULTS
A total of 30 patients who fulfilled the inclusion criteria and came for all the follow up visits were included. All the patients in group I and group II were diagnosed to have primary open-angle glaucoma.

- Group I included 15 patients who were treated with timolol 0.5% ophthalmic solution twice daily.
- Group II included 15 patients who were treated with bimatoprost 0.03% ophthalmic solution once daily at 9:00 pm.

The age of the patients in group I ranged between 40-80 years with a mean of 56.50 years, and in group II, the patients were between 40-74 years with a mean of 57.50 years.

There was no statistically significant difference between the mean age (p=0.726), gender and baseline IOP of the two groups.

The baseline mean IOP in group I was 22 mmHg. There was a statistically significant reduction in mean IOP at all subsequent visits (p<0.001). The baseline mean IOP in group II was 23.30 mmHg. There was a statistically significant reduction in mean IOP at all subsequent visits (p<0.001) (Figure 1).

The mean Tear Film Break-Up Time (TFBUT) in group I at baseline was 18 seconds. IT reduced to 10.7 seconds by the end of six months (p<0.001). The mean TFBUT in group II at baseline was 17.8 seconds. It reduced to 14.7 seconds by the end of 6 months (p<0.001) (Figure 2).

The mean Schirmer in group I at baseline was 26.1 mm. It reduced to 17 mm by the end of 6 months (p<0.001). The mean Schirmer in group II at baseline was 25.2 mm, it reduced to 21 mm by the end of six months (p<0.001). The mean reduction in Schirmer test by 6 months was 4.1 mm versus 9.1 mm in group I (Figure 3).

The rose bengal scores continued to rise over the period of 6 months in group I. The rise at 3 months and 6 months was statistically significant (p=0.002 and p<0.001), respectively. In group II, the increased rose bengal scores at 1 and 3 months were not statistically significant, while at 6 months, it was statistically significant (p=0.004).

For conjunctival impression cytology, all slides were examined and graded according to the staging of Natadasstra et al. The increase in grading by the 6th month was statistically significant in group I (p=0.002). However, the increase in grading by the 6 months was not statistically significant in group II (p=0.153) (Table 1).

### Table 1. Conjunctival Impression Cytology in Group I and II

<table>
<thead>
<tr>
<th>Study Visits</th>
<th>CIC - Number of Eyes</th>
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<tbody>
<tr>
<td></td>
<td>Stage 0</td>
</tr>
<tr>
<td>Group I</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>30</td>
</tr>
<tr>
<td>6 months</td>
<td>22</td>
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<tr>
<td>Group II</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>30</td>
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<tr>
<td>6 months</td>
<td>28</td>
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DISCUSSION
Over the last few years, the pace of advances in the evaluation and management of glaucoma has been truly breathtaking. With the advent of newer investigative modalities such as HRT, OCT and Gdx as well as FDT and short wavelength automated perimetry glaucoma is being diagnosed earlier than before in more people than before. It naturally follows that ophthalmologists are tempted to start antiglaucoma therapy earlier than before in an attempt to save the ever declining retinal nerve fibres. With such a choice of antiglaucoma medications available in the market, one relies on their potency, past experience with using these drugs and considers the cost factor when prescribing these medications. This study was undertaken to assess the efficacy and ocular surface effects of two potent drugs, which are frequently used as monotherapy in clinical practice.

In our study, in patients who were initiated on timolol, the IOP reduction over 6 months was 4.7 mmHg (21%). Thygesen et al found an IOP reduction of 6.2 mmHg (25.5%) for timolol after 28 days of treatment. After initiation of treatment with bimatoprost, it was observed that the mean reduction of IOP was 6.6 mmHg over 6 months. Other studies available in literature also show very significant reductions of IOP with bimatoprost. Cantor et al reported a decrease in IOP in the bimatoprost group from a baseline of 24.6 mmHg to 17.5 mmHg after 12 weeks (p<0.001).

The mean tear film break-up time in the timolol group at baseline was 18 seconds. It reduced to 10.7 seconds by the end of 6 months (p<0.001). In the study by Thygesen et al where TFBUT was assessed after timolol treatment for 28 days a decrease from 17.8 seconds on day 0 to 13.8 seconds on day 28 was seen.

The mean tear film break-up time in the bimatoprost group at baseline was 17.8 seconds. It reduced to 14.7 seconds at the end of 6 months (p<0.001). The mean reduction was 3.1 seconds. Alagoz et al in their study on bimatoprost and its effect on the ocular surface didn't find any statistically significant decrease in TFBUT over 6 months. The mean reduction in TFBUT was greater in the timolol group at both 3 months and 6 months when compared to reduction in the bimatoprost group, the difference was statistically significant (p<0.001).

The mean Schirmer’s in the timolol group at baseline was 26.1 mm. It reduced to 17 mm by the end of 6 months (p<0.001). The mean reduction in Schirmer’s by 6 months was 9.1 mm (35%). Kamath et al found a significant decrease in Schirmer’s value in patients on timolol (38%) at the end of one year treatment suggesting that long-term use of timolol is likely to affect tear secretion.

The mean Schirmer’s in the bimatoprost group at baseline was 25.1 mm. It reduced to 21 mm by the end of 6 months (p<0.001). The mean reduction in Schirmer’s by 6 months was 4.1 mm. Alagoz et al in their study on bimatoprost and its effect on the ocular surface didn’t find any statistically significant decrease in Schirmer’s values over 6 months. The mean reduction in Schirmer’s was greater in the timolol group at both 3 months and 6 months and it was statistically significant.

The rose bengal scores continued to rise over the period of 6 months in the timolol group. In the bimatoprost group, increase in scores were seen later towards the 6 months. While comparing the two groups, timolol was associated with significant increase in scores, however, the scores remained under 4, hence were not considered pathological. Thygesen et al in their comparison of timolol versus latanoprost assessed rose bengal scores over a period of 28 days. They found no statistically significant difference between the groups.

In our study, there were significant changes in conjunctival impression smears in the timolol group after 6 months. The number of goblet cells decreased over 6 months in 26% patients while this occurred in only 6% patients in the bimatoprost group. Kamath et al in their study...
found at the end of 6 months reduced goblet cell density in 6 (28%) patients from timolol group and two (9%) patients in the latanoprost group. They on correlation found that the decrease in goblet cell density was seen in conjunctival impression cytology specimens of patients with decrease in Schirmer’s and TFBUT values, which explains the reason for changes in these values.

Treatment-related adverse effects were observed in both the groups over the 6 months. The most frequent complaint was irritation followed by burning sensation, then blurring of vision. The symptoms however were mild in all the patients and persisted till the end of the study period, but were not severe enough for the patient to discontinue therapy.

CONCLUSION
This six month study demonstrated that both timolol and bimatoprost provide effective lowering of IOP in patients with POAG throughout the day, besides being safe and well tolerated. Both the drugs can thus be useful as first line therapy in the management of patients with POAG. Moreover, bimatoprost provided significantly better mean IOP reduction after 6 months of therapy as compared to timolol at all visits. The effect on the ocular surface is more with timolol as compared to bimatoprost and may warrant the addition of a tear substitute as a routine to provide comfort, clarity of vision to patients on timolol.

REFERENCES