

Incidence of hyperemia associated with bimatoprost treatment in naïve subjects and in subjects previously treated with latanoprost

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PURPOSE. *Bimatoprost is a potent hypotensive drug used in the treatment of glaucoma or ocular hypertension with lower target intraocular pressure (IOP) than latanoprost. Its most disturbing side effect is conjunctival hyperemia. The authors compared the extent of conjunctival hyperemia in patients receiving bimatoprost as initial therapy with that in patients whose treatment with latanoprost was replaced by bimatoprost.*

METHODS. *One group of consecutive patients with newly diagnosed bilateral primary open-angle glaucoma (POAG) was treated with once daily bimatoprost 0.03% ophthalmic solution as initial therapy. Treatment in another group of patients who had been on latanoprost treatment for at least 3 months was replaced by bimatoprost 0.03%. Conjunctival hyperemia was assessed by a single masked observer using a five-point grading scale.*

RESULTS. *The mean \pm SD baseline hyperemia scores were 0.4 ± 0.3 and 0.70 ± 0.3 for the first-line and replacement groups, respectively. Following 3 weeks of treatment, the mean post-treatment conjunctival hyperemia scores were 2.3 ± 1 and 1.1 ± 0.5 , respectively. IOP of 25.2 ± 9.8 mmHg and 18.95 ± 2.1 mmHg dropped to 18.79 ± 2.13 mmHg and 18.23 ± 1.95 mmHg, respectively, following bimatoprost therapy. The differences in baseline levels of hyperemia for each group were not statistically significant ($p=0.478$). Changes in hyperemia scores from baseline were highly significant ($p<0.001$) only in first-line therapy patients ($p=0.02$ for the replacement group).*

CONCLUSIONS. *The above findings suggest that patients already on prostaglandin therapy may be less likely to experience an increase in conjunctival hyperemia induced by bimatoprost. (Eur J Ophthalmol 2009; 19: 400-3)*

KEY WORDS. *Hyperemia, Bimatoprost, Latanoprost, Glaucoma*

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INTRODUCTION

Prostaglandin analogs have become an attractive and widespread choice of therapy for glaucoma and ocular hypertension. Their relatively lower incidence of adverse systemic effects combined with a high level of potency have encouraged their use as both first-line and adjunctive therapy. Latanoprost is associated with a high rate

of non-response in treated glaucoma patients, while bimatoprost is a potent hypotensive drug used in the treatment of glaucoma or ocular hypertension with lower target intraocular pressure (IOP) (1).

Conjunctival hyperemia is a frequent ocular adverse effect which is shared by all compounds of this class, with its highest incidence seen in patients on bimatoprost (approximately 45% of eyes) compared to 21% with la-

tanoprost (1). A great number of patients discontinue bimatoprost because of conjunctival hyperemia, despite the fact that it is usually transitory. In terms of efficacy, latanoprost, bimatoprost, and travoprost are considered as being equivalent in their ocular hypotensive effect (2). Some studies (3), however, have claimed that bimatoprost may have superior diurnal control. It has also been shown that bimatoprost allows more patients to reach target IOP when used as a replacement for latanoprost (4, 5). As such, some patients with glaucoma who are currently on latanoprost treatment may benefit from replacement by bimatoprost. For them, special attention must be paid to the potential adverse effect of bimatoprost on conjunctival hyperemia since this may be the deciding factor in the success of the treatment. Given the high non-response rate with latanoprost, it is important to know the incidence of hyperemia associated with the use of the more effective agent, bimatoprost, especially when it replaces latanoprost treatment.

The present study compared conjunctival hyperemia in patients receiving bimatoprost as first-line therapy with patients whose treatment with latanoprost was replaced by bimatoprost.

METHODS

This study was performed in accordance with the ethical standard of the Helsinki declaration and was approved by the IRB committee of the Tel Aviv Sourasky Medical Center (Helsinki Ethics Committee). All patients signed informed consent forms prior to volunteering their participation in the study.

One group of consecutive patients with newly diagnosed bilateral primary open angle glaucoma (POAG) began initial therapy with once daily bimatoprost 0.03% ophthalmic solution in both eyes. Another group of consecutive patients who had been on latanoprost 0.005% treatment in both eyes for at least 3 months had their treatment regimen replaced by bimatoprost 0.03%. Excluded were patients with known hypersensitivity or previous treatment with bimatoprost, those with a documented history of ocular infection or inflammation within the previous 3 months, and those with histories that suggested any problems with hyperemia in the past that had led to a change in glaucoma treatment.

There was no washout period following the cessation of latanoprost. All the study patients were instructed to instill

the drops of bimatoprost once daily at 8:00 PM. No other ocular therapy was permitted. Conjunctival hyperemia was assessed by a single masked observer using a five-point hyperemia grading scale using five different photographs for hyperemia matching: 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe. Fractionated grades (0.5, 1.5, et cetera) were allowed. Only the scores for the right eye were used for analysis. The observer was masked to the IOP of the participants. Hyperemia was assessed prior to initiation of initial and replacement therapy and 3 weeks thereafter. Statistical significance between pre- and post-treatment hyperemia scores was determined by the paired and unpaired Student *t* test. Significance was set at $p < 0.05$.

RESULTS

The study population consisted of 36 patients diagnosed with POAG. The initial bimatoprost group included 9 men and 9 women (mean age 64.5 years, range 35–82 years). The replacement group included 10 men and 8 women (mean age 67.4 years, range 41–81 years). The demographic characteristics were similar for both study groups. The mean \pm SD hyperemia scores at baseline were 0.4 ± 0.3 and 0.70 ± 0.3 , respectively, and 2.3 ± 1 and 1.1 ± 0.5 following 3 weeks of treatment, respectively (Table I). The mean \pm SD baseline (IOP) levels were 25.2 ± 9.8 mmHg and 18.95 ± 2.1 mmHg, and they were 18.79 ± 2.13 mmHg and 18.23 ± 1.95 mmHg following bimatoprost treatment, respectively. The differences in baseline hyperemia (first visit of the latanoprost patients before replacement and before treatment for the first-line group) were not significant ($p = 0.478$). Changes in hyperemia scores between baseline and post-treatment were significant ($p < 0.001$) in the initial bimatoprost patients (also, $p = 0.02$ before versus after treatment for the replacement group).

TABLE I - MEAN CONJUNCTIVAL HYPEREMIA SCORES

	Baseline hyperemia	Post-treatment hyperemia
Initial therapy	0.4 ± 0.3 SD	2.3 ± 1.0 SD
Replacement therapy	0.7 ± 0.3 SD	1.1 ± 0.5 SD

$p < 0.001$ (0.4 ± 0.3 compared to 2.3 ± 1.0); $p < 0.000$ (2.3 ± 1.0 compared to 1.1 ± 0.5).

DISCUSSION

The exact mechanism by which prostaglandin analogs cause conjunctival hyperemia is not fully understood. Prostaglandin F_{2α} (PGF_{2α}) is itself considered to be a potent proinflammatory agent and, as such, it may be that its derivatives and analogs cause hyperemia by direct induction of inflammatory mediators. Bimatoprost, unlike the PGF_{2α} analogs (latanoprost and travoprost), is a fatty acid with an ethyl amide at the C-1 carbon of the alpha chain, similar to the class of fatty acid amides known as prostamides. Despite these clear pharmacologic differences, some studies (6) suggest that the IOP reduction seen with bimatoprost does, in fact, result from direct PGF receptor activation by the free fatty acid, rather than by its distinctive quality as a prostamide.

In this small case series, changing glaucoma therapy from latanoprost 0.005% to bimatoprost 0.03% was associated with less conjunctival hyperemia than that measured in patients in whom bimatoprost 0.03% was used as first-line therapy. The decreased hyperemic response seen in the replacement therapy group may be a consequence of desensitization at the level of the PGF-receptor. Prior treatment with latanoprost may have had a desensitizing effect on the PGF-receptor which subsequently also diminished its adverse hyperemic effect. This may explain why we found less hyperemia in the replacement group than in the initial therapy group. The fact that hyperemia is a transitory complaint, even in patients who receive bimatoprost as monotherapy, may imply that a similar desensitization process occurs by the use of the drug itself. One potentially disturbing factor that emerged in this study is that baseline hyperemia may not be truly masked since latanoprost itself causes hyperemia: if hyperemia had been detected during baseline examination, suspicion could arise that the patient had received latanoprost before. Since adverse effects are integral to any drug used in a clinical study, it is for the precise reasons mentioned above that latanoprost was chosen as the drug to be replaced in the current study. Notably, the difference in baseline hyperemia scores at study onset between initial and former latanoprost-treated patients was not significant ($p=0.478$) so the chances of an observer bias remain very slight. Although the difference between pre- and post-treatment in the replacement group reached a level of significance ($p=0.02$), the clinical importance of this finding is negligible.

The desensitization theory that we propose above war-

rants further investigation. A recent in vitro study (7) of the inflammatory potential and toxicity profile of latanoprost, travoprost, and bimatoprost failed to demonstrate direct activation of the inflammatory pathways involving major inflammation-related markers. Thus, alternate explanations for the conjunctival hyperemia need to be considered.

Conjunctival hyperemia may be caused by vasodilatation related to the production of nitric oxide (NO) (8). Possible induction of NO synthase by the prostaglandin analogs may be responsible for the observed hyperemia, but the exact mechanism by which this occurs remains elusive. An analogous "desensitization" theory for NO synthase could similarly offer an explanation for the reduced hyperemic response that occurred when bimatoprost replaced latanoprost, but this needs to be further studied as well.

An alternate explanation for the conjunctival hyperemia may be related to the effect of the preservative benzalkonium chloride (BAC) present in all commercial preparations of latanoprost and bimatoprost used in this study. BAC has been shown to have a potent dose-dependent toxic effect resulting from the interaction of the quaternary ammonium with cell membranes and cell-defense mechanisms (7). It should be noted that latanoprost contains the highest concentration of BAC but seems to cause the lowest incidence of hyperemia when used as single therapy. One possible explanation for this observation is that the direct cytotoxic effect of the BAC may impair the cellular inflammatory response and diminish the associated vasodilatation. In our patients, prior treatment with latanoprost (in combination with BAC) may have diminished the local cellular inflammatory potential and subsequently dampened the associated hyperemic effect of bimatoprost. BAC has been shown in vitro to cause decreased expression of adhesion molecules (CD31 and CD54), most likely as a result of toxic apoptonecrosis of conjunctival cells (7).

The results of the current study suggest that replacement therapy with bimatoprost 0.03% results in less conjunctival hyperemia than when bimatoprost 0.03% is given as initial glaucoma therapy. Consequently, patients who are already on prostaglandin analog therapy, such as latanoprost 0.005%, may be more disposed to replacement medication and may better tolerate future replacement by bimatoprost 0.03%. This result is important for a number of reasons: first, there is a high rate of nonresponders to latanoprost, and secondly, ophthalmologists need not be concerned about side effects, such as hyperemia, when

replacing latanoprost by bimatoprost because patients are less likely to develop hyperemia while very likely benefiting from a more powerful agent that causes lower target pressures. We did not directly measure our patients' compliance in using the drops, but the significant reduction of IOP in the initial therapy group as well as the sustained IOP level in the replacement group can serve as indirect indicators of their compliance.

One of the limitations of this study is that it was not possible to carry out a power analysis. Despite the shortcomings of this study—mainly a relatively small number of patients and a short follow-up period and varying durations of latanoprost treatment in the second-choice group—we believe that the above findings are of considerable clinical relevance. There is the possibility that many patients who had developed hyperemia actually stopped the drug early and were not included. This may have resulted in the inclusion of some patients who were inherently less likely to suffer from hyperemia.

The multitude of glaucoma medications now available for use allows treatment to be tailored to the individual patient in order to maximize effect and increase compliance. Conjunctival hyperemia has significant implications on patient comfort and subsequent compliance with medications. Moreover, chronic hyperemia and conjunctival irritation may cause local histologic changes that may interfere with future success of filtering surgery. The consecutive nature in which patients were entered into this study al-

lows for an authentic clinical comparison. Every glaucoma practice consists of a multitude of patients, some of whom may be prone to develop hyperemia or who have undergone treatments that had been modified according to therapeutic effect or adverse reactions.

Patients should still be warned of the possibility of hyperemia as well as other potential adverse effects associated with the use of bimatoprost. The findings of this study, however, suggest that those already on prostaglandin therapy will benefit more from its use as replacement therapy. Since latanoprost is associated with a high rate of nonresponding glaucoma patients, bimatoprost can serve as an alternative treatment without aggravating hyperemia in patients with glaucoma or ocular hypertension.

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