CONJUNTIVAL HYPEREMIA WITH THE USE OF A FIXED COMBINATION OF LATANOPROST/TIMOLOL: SYSTEMATIC REVIEW AND META-ANALYSIS OF CLINICAL TRIALS

DESARROLLO DE HIPEREMIA CONJUNTIVAL TRAS EL EMPLEO DE LA COMBINACIÓN FIJA DE LATANOPROST/TIMOLOL: REVISIÓN SISTEMÁTICA Y METAANÁLISIS DE ENSAYOS CLÍNICOS PUBLICADOS

VINUESA-SILVA JM1, VINUESA-SILVA I2, PINAZO-DURÁN MD3, SOTO-ÁLVAREZ J4, DELGADO-ORTEGA L5, DÍAZ-CEREZO S5

ABSTRACT

Purpose: To assess the association of conjuntival hyperemia with the use of a fixed combination of latanoprost/timolol, through a systematic review and meta-analysis of clinical trials in patients with glaucoma.

Methods: A systematic review of published clinical trials of latanoprost/timolol and other competitors was conducted in Medline, Embasse and Cochrane Controlled Clinical Trials Register, between 2000 and 2007. Statistical analysis included calculation of the odds ratio (OR) with its 95% confidence interval (CI) using the fixed effects model of Mantel-Haenszel and the random effects model of Der Simonian and Laird. To assess the heterogeneity between trials the Cochran Q test and the $I^2$ rate were calculated. The conjunctival hyperemia rates obtained were compared with the Chi-square test.

Results: A total of 8 clinical trials comparing latanoprost/timolol fixed combination with different

RESUMEN

Objetivo: Valorar la asociación de hiperemia conjuntival con el uso de la combinación fija de latanoprost/timolol en el tratamiento del glaucoma, a través de una revisión sistemática y de un metaanálisis.

Métodos: Se efectuó una búsqueda de los ensayos clínicos publicados de latanoprost/timolol y distintos comparadores en las bases de datos Medline, Embasse y Cochrane Controlled Clinical Trials Register, entre 2000 y 2007. La medida para valorar el tamaño del efecto ha sido la odds ratio (OR) y su intervalo de confianza (IC) del 95 %, habiéndose calculado mediante el modelo de efectos fijos de Mantel-Haenszel y el de efectos aleatorios de Der Simonian y Laird. Para valorar la existencia de heterogeneidad entre los estudios, se llevó a cabo la prueba Q de Cochran así como el cálculo del índice $I^2$. Los porcentajes de hiperemia hallados se han comparado a través de la prueba de Chi-cuadrado.
therapeutic options were found. As trial heterogeneity was moderate (Q: 14.64; df=7; p=0.041; $I^2=52.2\%$) a random effects model was used. The final OR was 0.47 (CI 95%: 0.24-0.90); p = 0.024. The total conjunctival hyperemia incidence was 2.9% in the latanoprost/timolol group and 7.0% for the competitors (p<0.0001).

**Conclusions:** The use of a fixed combination of latanoprost/timolol is associated with a significant reduction (53%; CI 95%: 10%-76%) in the development of conjunctival hyperemia against the other compared options for the treatment of glaucoma (Arch Soc Esp Oftalmol 2009; 84: 199-208).

**Key words:** Conjunctival hyperemia, glaucoma, latanoprost, timolol, meta-analysis.

**INTRODUCTION**

According to the World Health Organization (WHO), glaucoma is the second cause of blindness in developed countries, affecting 60 million people. It is believed that 50% of all glaucoma cases are yet to be diagnosed (1). The prevalence rates increase in proportion to age (2-4) and it is estimated that the prevalence in the general population is of approximately 2%. But if we focus on the population over 50, this percentage rises to 3%, with 23% of glaucoma patients being over 75.

An early diagnostic is crucial to prevent the progression of the disease, but this is difficult because glaucoma is initially painless and free of symptoms. The goal would be to identify individuals in the initial stage of the disease and those who are susceptible of developing it and exhibit risk factors such as family history, high myopia, diabetes, high blood pressure, age and increase of intra-ocular pressure (IOP) (5).

Pharmacological treatments are based on the reduction of IOP in order to delay or prevent the progression to glaucoma in patients with high IOP or to slow down its development in those patients who already have it (6). The pharmacological treatment of choice is topical and, as glaucoma is a chronic disease, the treatment must be permanent together with regular IOP and visual field checkups (7,8). Accordingly, when choosing a treatment, it is essential to take into account not only the efficiency and safety of the drug but also the ability of the patient to comply with the treatment on a permanent basis, because the patients who interrupt treatment exhibit an increase of IOP which could lead to a further development of the disease towards blindness (9).

At present, the European Glaucoma Society (EGS) recommends monotherapy as a first line of treatment with a topical pressure-reducing agent selected on the basis of the efficiency and safety profile and also on the patients quality of life, the cost and compliance. If a drug does not achieve a target IOP level it must be substituted and, if monotherapy does not achieve that desired level, several drugs must be associated (7,8).

Patient compliance with the treatment depends on many factors (satisfaction with the treatment, cost, ease of application, knowledge about the disease and the consequences of interrupting treatment), but mainly on the secondary local and systemic effects that the drug may cause (10). If we compare beta blockers with prostaglandins, the former exhibit very few local effects but can cause important systemic effects such as worsening of bronchial asthma, chronic obstructive pulmonary disease, heart insufficiency and bradycardiac arrhythmia, among others. In the case of prostaglandins the opposite occurs: They hardly exhibit a systemic effects but the local effects can include conjunctival hyperemia, iridian pigmentation, bloating of the eyelids, keratitis punctata, anterior uveitis and cystoid macular edema (11).
Conjunctival hyperemia is the most common secondary effect of prostaglandins (12) and must be considered by ophthalmologists because it can give rise to non-compliance with the treatment (13). Due to the importance of this adverse effect and considering that the association of a prostaglandin with timolol is one of the most utilized second line treatments, the objective of this study was to carry out a systematic revision and a meta-analysis of the clinical trials published to date, comparing the hyperemia effects produced by the combination of latanoprost/timolol against other possible treatments (latanoprost and timolol separately and other pressure reducing drugs) in patients with high ocular pressure or glaucoma.

**SUBJECTS, MATERIAL AND METHODS**

**Search strategy**

Articles were identified searching for clinical trials published in Medline, Embase and Cochrane Controlled Clinical Trials Register between 2000 and 2007 which compared the fixed combination of latanoprost/timolol vis-à-vis other therapeutic options for treating glaucoma or high IOP.

The search utilized the following keywords: glaucoma, high intra-ocular pressure, randomization, clinical trials, latanoprost/timolol and conjunctival hyperemia.

**Selection of studies**

Two independent researchers searched for published papers and selected relevant articles according to the criteria established for the inclusion of published studies in the systematic review, as follows: a) Comparative clinical trials (excluding crossed designs); b) existence of an active control in the trial; c) assessment of the prevalence of conjunctival hyperemia due to treatments.

To assess the articles found, the title and summary was review first to determine whether they fulfilled the inclusion criteria. The articles which initially passed this filter were reviewed in full to make sure they complied in tightly with the inclusion criteria and therefore could be included in the systematic revision.

**Extraction of data**

The two researchers carried out the extraction of data filling in a codification sheet designed specially for the revision. In addition, they evaluated the methodological quality of the included triumphs as described below. All the identified differences were discussed and resolved by agreement between both researchers. When agreement was not possible, they requested the intervention of a third researcher.

A table was designed for summarizing the information obtained of each selected article, comprising the trial authors, the treatment assessed, the comparing treatment, the number of patients in which the degree of hyperemia was evaluated, their mean age and the percentage of hyperemia exhibited in each group of patients.

**Evaluation of quality**

The researchers determined the quality of the included documents utilizing the Jadad scale (14). This is a validated instrument in which the documents are given a score between zero and eight according to the following characteristics: randomization (one or two points depending on whether the method utilized is described), masking (one or two points depending on whether the method utilized is described), described inclusion and exclusion criteria (one point), details of abandonment or cancellations (1 point) and description of adverse effect evaluation methods (1 point). The end result provides an estimation of the validity of the clinical trials utilized for developing the meta-analysis: The higher the score, the higher the validity and reliability of the trial.

**Statistical analysis**

The entire statistical analysis of the data included in the meta-analysis was carried out with the program «Comprehensive Meta-Analysis» version 2.2 (Biostat, Inc., Englewood, New Jersey; www.meta-analysis.com).

Heterogeneity between trials was analyzed using the Q for Cochran test and the index I² calculation which allowed us to determine the way in which possible existing heterogeneity could affect the conclusions of the meta-analysis (15). The values of I²
of 50% or more indicate a considerable level of heterogeneity. For the Q for Cochran test, statistical significance was set at p < 0.1 instead of p < 0.05 due to the low contrast power when the number of studies included is low.

To assess the size of the effect the odds ratio (OR) was utilized. The OR of the various clinical trials were combined utilizing the fixed effect model of Mantel-Haenszel (for homogeneous clinical trials) (16) and the random effect model of Der Simonian and Laird (for heterogeneous clinical trials) (17). The results obtained were represented in a forest plot type graph, showing the OR values with the corresponding confidence interval of 95% for each individual study and the global or aggregate value for the meta-analysis, establishing a statistical significance starting with p<0.05.

The possible publication bias was assessed with the visual inspection of the funnel plot. This graph ordered the results on the basis of the precision of its measurements and allows us to determine the existence of studies with low precision and extreme results biased towards or against the latanoprost/timolol products. If we only observe extreme results of studies with low precision (generally with a small sample of subjects) biased towards latanoprost/timolol but not towards the comparator group, we could concluded that studies with negative results do exist but have not been published. When the samples are small, the random error of the study is high and therefore the results should go for and against (due to the random effect). When there is no publication bias, the points on the graph tends to form an inverted funnel. If, on the contrary, said bias exists, the group of points will appear deformed at one of its ends (18).

In order to analyze the robustness of the results and verify whether any of the studies is having a decisive influence, a sensitivity analysis was made extracting systematically and separately each one of the clinical trials included in the meta-analysis. If the results thus obtained are similar both in direction and in magnitude of the effect and statistical significance, we may conclude that the analysis is robust.

The QUORUM guide has been followed (Quality of Reporting of Meta-analysis) to present and discuss the results of the meta-analysis (19).

In addition, the frequency of appearance of hyperemia was calculated for each group (latanoprost/timolol and the rest of comparators), calculating the existence of statistically significant results by means of the Mantel Haenszel Chi square test. The degree of intensity of the possible association between the appearance of hyperemia and the treatment utilized was calculated by the relative risk estimation (RR) pondered utilizing the Mantel Haenszel method (the most adequate method in the case of estimations with a low number of subjects, as is the case with our study) (20). Said calculations were carried out with the SPSS v.14 statistical analysis software.

RESULTS

Literary search

19 articles assessing the latanoprost/timolol association against other therapeutic options were identified as potential candidates for inclusion in the meta-analysis. Of these, 11 articles were excluded according to the above-mentioned exclusion criteria: 2 were not clinical trials (21,22), 1 did not have active control (23), 5 were crossed design clinical trials (24-28) and the remaining three did not record the prevalence of hyperemia (29-31). The match between the two researchers as regards the inclusion of the studies in the analysis was good (Kappa index = 0.8). The discrepancies were resolved by the third researcher.

Finally, eight clinical trials remained for inclusion in the meta-analysis, all of which included patients with ocular hypertension or glaucoma and provided specific hyperemia data for a total of 2600 patients (32-39). The flow of the analysis of the included and excluded clinical trials is as shown in figure 1.

Characteristics of the trials

Table I shows the characteristics of the clinical trials included in a meta-analysis.

At the beginning of the trials there was a randomized population of 2511 patients that were assessed during a mean period of 4.72 months (min=21 days, max= 12 months). Of these, 1761 patients were diagnosed with open angle glaucoma, 549 had intra-ocular hypertension and 201 other types of glaucoma. In the course of the clinical trials, the sum of patients of which conjunctival hyperemia
data were obtained and which were considered in this meta-analysis was 2600. Of these, 1156 were treated with a fixed combination of latanoprost/timolol and the rest were treated with the various comparators: 460 only with latanoprost, 289 only with timolol, 50 only with travoprost, 162 with the non-fixed combination of brimonidine and timolol, 254 with the non-fixed combination of latanoprost and timolol, 22 with the non-fixed combination of travoprost and brinzolamide and 207 with the fixed combination of travoprost and timolol.

The frequency of appearance of hyperemia pondered by a number of subjects in each study was of 2.9% in the latanoprost/timolol group and of 7.0% in the comparator group; p<0.0001.

As statistically significant differences were found, the RR pondered with the Mantel Haenszel method was carried out: RR = 0.44 (IC 95%; 0.30-0.63); p=0.00001. Consequently, the utilization of latanoprost/timolol reduces the risk of hyperemia in 56% compared with the utilization of the comparators analyzed in our study.

Results of the meta-analysis

The Q for Cochran indicated a certain degree of heterogeneity between the studies (Q = 14.64; p = 0.041). This finding was confirmed by the value of the $I^2$ index = 52.2%, which indicated the existence of moderate heterogeneity. In the face of these values, the final OR calculation was done utilizing the random effect model, which is more conservative and takes into account heterogeneity. The results indicate that the use of the fixed combination of latanoprost/timolol vis-à-vis other comparators was associated to a lower percentage of conjunctival hyperemia (OR = 0.467; 95% CI: 0.242 – 0.905, p = 0.024). The OR of each study and the combined final OR calculated with both statistical models (fixed and random effects) are shown in figure 2.

Sensitivity Analyses

The sensitivity analyses indicated that the mean aggregate OR could range between 0.39 and 0.50 depending on the clinical trial excluded of the meta-analysis. None had a significant impact in the global calculation of OR because in all cases the latanoprost/timolol exhibited a degree of hyperemia significantly lower than the comparator group (table II).

Bias of the publications

On the basis of the visual analysis of the funnel plot which orders the studies according to the precision of their measurement, no bias evidence was found (fig. 3) because six of the eight studies were within the funnel area we could not appreciate an important asymmetry.

DISCUSSION

At present, a fixed combination of two drugs is increasingly utilized in patients that require more than one drug to reach the target IOP. This facilitates treatment compliance and therefore its efficiency (40). The differences which may arise in compliance according to the different fixed combinations could be related to the secondary effects they cause. In the case of combinations including...
prostaglandin, the degree of hyperemia produced could be a crucial factor when selecting a treatment.

The literature describes that, of the three prostaglandin equivalents in the market (latanoprost, bimatoprost, and travoprost), latanoprost is the one which produces the least conjunctival hyperemia when administered in monotherapy (41,42).

The results of this meta-analysis suggest that the use of a fixed combination of latanoprost/timolol is associated to a lower degree of hyperemia than the rest of alternatives utilized as comparators in the various clinical trials that have been published.

As this meta-analysis includes only one clinical trial which compares latanoprost/timolol with travoprost/timolol and no evaluation between

Table I. Main characteristics of the clinical trials included in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Assessed Treatment</th>
<th>Control Group</th>
<th>Number of Patients</th>
<th>Patients with hyperemia</th>
<th>Duration*</th>
<th>Mean pondered Age</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfeiffer N (30)</td>
<td>LT/TM</td>
<td>LT ; TM</td>
<td>LT/TM = 140</td>
<td>2.86%</td>
<td>6 m</td>
<td>64</td>
<td>7</td>
</tr>
<tr>
<td>Higginbotham EJ, et al (31)</td>
<td>LT/TM</td>
<td>LT ; TM</td>
<td>LT/TM = 138</td>
<td>7.97%</td>
<td>6 m</td>
<td>62</td>
<td>8</td>
</tr>
<tr>
<td>Olander K, et al (32)</td>
<td>LT/TM</td>
<td>LT</td>
<td>LT/TM = 175</td>
<td>0.6%</td>
<td>21 d</td>
<td>64</td>
<td>8</td>
</tr>
<tr>
<td>Franks WA, et al (33)</td>
<td>LT/TM</td>
<td>TR</td>
<td>LT/TM = 56</td>
<td>1.8%</td>
<td>9.3%</td>
<td>N=37; c65</td>
<td>6</td>
</tr>
<tr>
<td>Garcia-Sánchez J, et al (34)</td>
<td>LT/TM</td>
<td>BR and TM</td>
<td>LT/TM = 163</td>
<td>0.61%</td>
<td>2.47%</td>
<td>N=69; 265</td>
<td>5</td>
</tr>
<tr>
<td>Diestelhorst M, et al (35)</td>
<td>LT/TM</td>
<td>LT and TM</td>
<td>LT/TM = 262</td>
<td>3.1%</td>
<td>8.7%</td>
<td>65</td>
<td>8</td>
</tr>
<tr>
<td>Martinez de la Casa JM, et al (36)</td>
<td>LT/TM</td>
<td>TR and BZ</td>
<td>LT/TM = 22</td>
<td>13.6%</td>
<td>18.2%</td>
<td>65</td>
<td>5</td>
</tr>
<tr>
<td>Topouzis F, et al (37)</td>
<td>LT/TM</td>
<td>TR/TM</td>
<td>LT/TM = 200</td>
<td>2.5% 15.0%</td>
<td>12 m</td>
<td>65</td>
<td>8</td>
</tr>
</tbody>
</table>

Dose utilized in clinical trials: monotherapy: (Latanoprost (LT) = 0.005%. Timolol (TM) = 0.5%. Travoprost (TR) = 0.004%. Brimonidine (BR) = 0.2%. Brinzolamide (BZ = 0.1%) and combinations (LT/TM = 0.005/0.5%, TR/TM = 0.004/0.5%).

Fig 2. The vertical line that goes through 1 represents the value of the null effect, showing at the left the studies with results in favor of the latanoprost/timolol group and at the right the studies with results in favor of the comparator group of other treatments.
Latanoprost/timolol and bimatoprost/timolol, it cannot be concluded that the fixed combination of latanoprost/timolol is associated to a lower appearance of hyperemia vis-à-vis the other two fixed combinations of prostaglandin equivalent and timolol.

Until more evidence is available on the appearance of hyperemia with the use of a fixed combination of bimatoprost/timolol and travoprost/timolol, the results of this meta-analysis suggest that, to this date, the best alternative when it is necessary to utilize a combination of prostaglandin equivalents and timolol is the latanoprost/timolol combination.

One of the limitations of this study is that only eight clinical trials have been included and that the comparator group could vary in each. This might increase the heterogeneity of the included studies. Due to this degree of heterogeneity encountered in the studies, the conclusions of this meta-analysis should be interpreted prudently until more comparative clinical trials assessing the appearance of hyperemia with the use of different fixed associations of prostaglandins and timolol are made available.

A further limitation of this study (and of any systematic revision) is the possibility of excluding some published study based on the same topic. A comprehensive search in various databases (Medline, Embase and Cochrane Controlled Clinical Trials Register) and the exclusion of a restriction bias (per publication type or language) has endeavored to minimize this effect. The search period (2000-2007) covers any possible publication taking into account the dates on which fixed combination antiglaucoma drugs were launched.

As regards the existence of a possible publication bias in which the studies with negative results might not have been published, the funnel plot did not give any indication that this could have occurred, even though the usefulness of this plot is limited when the number of studies is small.

The results obtained in this study have focused on analyzing the degree of hyperemia exhibited by latanoprost/timolol vis-à-vis a group of possible drugs in fixed or non-fixed combination. If a group of clinical trials is available in the future with the same comparator group, it would be interesting to carry out this meta-analysis again, but focusing it on face-to-face comparisons which at this time were not possible.

To conclude, this meta-analysis has shown that the fixed combination of latanoprost/timolol exhibits an advantage vis-à-vis the existing alternatives because it significantly reduces the degree of hyperemia which the patients might experience as a side effect of the treatment. This adverse effect should be taken into account together with the efficiency data in order to improve compliance and the quality of life in a group of patients which must remain in lifelong treatment due to the chronic nature of glaucoma.
REFERENCES


27. Konstas AG, Kozobolís VP, Lallos N, Christodouläkis E, Stewart JA, Stewart WC. Daytime diurnal curve comparision between the fixed combinations of latanoprost 0.005%/timolol maleate 0.5% and dorzolamide 2%/timolol maleate 0.5%. Eye 2004; 18: 1264-1269.


35. Franks WA, Renard JP, Cunliffe IA, Rojanapongpun P. A 6-week, double-masked, parallel-group study of the efficacy and safety of travoprost 0.004% compared with latanoprost 0.005%/timolol 0.5% in patients with primary open-angle glaucoma or ocular hypertension. Clin Ther 2006; 28: 332-339.


37. Diestelhorst M, Larsson LF; European-Canadian Latanoprost Fixed Combination Study Group. A 12-week, randomized, double-masked, multicenter study of the fixed combination of latanoprost and timolol in the evening versus the individual components. Ophthalmology 2006; 113: 70-76.


39. Topouzis F, Melamed S, Danesh-Meyer H, Wells AP, Kozobolis V, Wieland H, et al. A 1-year study to compare the efficacy and safety of once-daily travoprost 0.004%/timolol 0.5% to once-daily latanoprost 0.005%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. Eur J Ophthalmol 2007; 17: 183-190.

