COST-EFFICACY ANALYSIS OF FIXED COMBINATIONS OF PROSTAGLANDIN/PROSTAMIDE FOR TREATING GLAUCOMA

ANÁLISIS COSTE-EFICACIA DE LAS COMBINACIONES FIJAS DE PROSTAGLANDINAS/PROSTAMIDA PARA EL TRATAMIENTO DEL GLAUCOMA

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ABSTRACT

Objective: To assess the cost-efficacy of three fixed-combination glaucoma treatments currently available in Spain [bimatoprost with timolol (BT) - Ganfort®, latanoprost with timolol (LT) - Xalacom®, and travoprost with timolol (TT) - DuoTrav®].

Methods: Because no studies are available that give a direct comparison of these drugs, a systematic review was carried out to assess their efficacy. Resource consumption and costs were estimated using a model of usual local practice. For each of the three drugs, average and incremental cost-efficacy ratios were determined in terms of euros per percentage point of reduction of intraocular pressure (IOP) over a three-month period.

Results: BT reduced IOP by 35.1%, LT by 35.0% and TT by 34.7%. Average cost-efficacy was estimated to be € 5.34 per percentage point of IOP reduction with BT, € 5.40 with LT, and € 5.45 with TT. Incremental cost-efficacy (incremental cost per incremental percentage point of IOP reduction) was estimated to be € 94.65 for LT vs. TT, and was negative for BT vs. TT and BT vs. LT, since in both cases BT was more efficacious and less expensive.

RESUMEN

Objetivo: Evaluar la relación coste-eficacia de las tres combinaciones fijas de prostaglandinas/prostamida con timolol actualmente disponibles en el mercado español [bimatoprost con timolol (BT) - Ganfort®, latanoprost con timolol (LT) - Xalacom® y travoprost con timolol (TT) - DuoTrav®].

Métodos: Dado que no existen estudios que comparen de una manera directa la eficacia de estos fármacos, se llevó a cabo una revisión sistemática de la evidencia indirecta en lengua inglesa. Se estimaron el consumo de recursos sanitarios y su coste a partir de un modelo esquemático de la práctica clínica habitual en nuestro medio. Se calcularon para cada fármaco la relación coste-eficacia media y la relación coste-eficacia incremental, en términos de euros por punto porcentual de reducción de presión intraocular (PIO) en un periodo de tres meses.

Resultados: BT redujo la PIO en un 35,1%, LT en un 35,0% y TT en un 34,7%. El coste-eficacia medio se estimó para BT en € 5,34 por punto porcentual de reducción de PIO, para LT en € 5,40 €, y para TT en € 5,45 €. El coste-eficacia incremental (coste adicional por punto porcentual adicional de
**Conclusions:** Compared to travoprost/timolol and latanoprost/timolol, bimatoprost/timolol appears to be the most economic alternative, with equal or better efficacy and safety results (*Arch Soc Esp Oftalmol* 2008; 83: 595-600).

**Key words:** Glaucoma, cost analysis, beta-blocker, prostaglandin analogue, fixed combinations.

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**INTRODUCTION**

Primary open-angle glaucoma (POAG), the most common form of glaucoma, is a chronic and progressive optical neuropathy that is one of the main causes of blindness in the Western world. It is characterized by a progressive loss of nervous fibers of the retina that could be associated with a painless elevation of intraocular pressure (IOP) and a loss of visual field. If not adequately treated, the natural course of this pathology could culminate in irreversible blindness (1).

Although there are considerable differences about the prevalence of glaucoma in literature, there is no doubt that it is a problem that affects a very large number of people, above all of an advanced age, and that it represents a high cost (2,3). The estimations in international studies vary between 0.4% and 8.8% of the population over 40 years, while in Spain the prevalence has been situated at 2% (4-6).

The exact etiology of POAG is unknown, but it is known that an increase of the IOP is the most important risk factor and for the moment, the only one that can be acted on. Different studies have shown a benefit both in high-tension and normal-tension glaucomas and in ocular hypertensives with the decrease of IOP (7-10). For this reason, the control of IOP is the main aim of glaucoma treatments. Nowadays medical treatment is the first line of action to reach the IOP objective in patients with POAG (11). Prostaglandin/prostamide analogs and the beta-blockers are the fist line of drugs, keeping anhydrase and alpha-agonist inhibitors as second line drugs.

However, recent studies have suggested that a combination of some of these drugs have higher benefits than the non fixed combinations. Particularly, the beta-blockers and prostaglandin analogs have mechanisms of complementary action, and firstly, drops that combine these therapies are beginning to gain popularity (12-15).

Fixed combinations improve the hypertensor efficacy, diminishing secondary effects, and allowing more comfortable guidelines with improved performance for patients, but they also have a greater cost. Given that resources in the National Health system are becoming more limited, cost-efficacy studies for these treatments are necessary. The present study aims to evaluate the cost-efficacy relationship of the three fixed combinations of prostaglandin/prostamide with timolole available on the Spanish market.

**SUBJECTS, MATERIAL AND METHODS**

The fixed combination of beta-blockers and prostanoid analogs presently available in Spain are bimatoprost 0.03% with timolole 0.50%, (BT) (Ganfort®, Allergan, Irvine, CA), latanoprost 0.005% with timolole 0.50%, (LT) (Xalacom®, Pharmacia, Kalamazoo, MI, and Pfizer, New York, NY), and Travoprost 0.004% with timolole 0.50%, (TT) (DuoTrav®, Alcon, Forth Worth, TX). Given that there are no studies comparing in a direct way the efficacy of these drugs, a systematic revision in English of the evidence was carried out.

The data on BT was obtained from two recent Studies with a total of 1,061 patients ([Katz LJ, Lewis RA, Batoosingo AL, Liu C, for the Ganfort® Investigators’ Group II. Bimatoprost/timolol appears to be the most economic alternative, with equal or better efficacy and safety results (*Arch Soc Esp Oftalmol* 2008; 83: 595-600).)]

**Palabras clave:** Glaucoma, análisis de costes, betabloqueante, análogo de prostaglandinas, combinaciones fijas.
Randomized Parallel Comparison to Its Individual Components in Patients With Glaucoma or Ocular Hypertension. ARVO 2007) y (Brandt JD, Cantor LB, Batoosingh AL, Liu C for the Ganfort® Investigators’ Group. A 3-Month, Randomized Study Comparing Bimatoprost/Timolole Fixed-Combination Therapy to Monotherapy With Bimatoprost or Timolole in Patients With Glaucoma or Ocular Hypertension. IGS 2007)]. In these Studies 533 patients were treated with BT, and the rest with individual components. The systematic revision identified four studies comparable with LT and TT (24-27), with data of a total of 1,484 patients (table I). the search criteria was: controlled double blind study, the same temporal horizon than in the BT trials, the same efficacy variable, period of washing before initial sight, and comparable age and basal values. The common primary efficiency indicators in the include trials were the difference between the IOP with treatment and the basal IOP, both averages in the morning, achieved in a period of three months. As the basal IOP was not identical in the different studies, the diminishing percentage was calculated for each case, as well as the efficacy variable used in the determination of cost-efficiency.

Starting from the schematic model of clinical practice (fig. 1), the cost associated with treatment with anti-glaucoma drugs was determined and the cost-efficiency relationship for each drug and the incremental cost-efficiency relationship were calculated. For this purpose, the average cost-efficiency relationship was defined as a result of dividing the cost of the treatment with the drug for its hypertensor efficacy. The incremental cost-efficiency relationship was made by dividing the additional treatment costs with the drug with respect to the most economic comparator for the additional efficacy against the same comparator.

**Fig. 1: Schematic model of clinical practice.**

\[
\text{Mean cost-efficiency of treatment A} = \frac{\text{cost of treatment A}}{\text{Efficacy of treatment A}} \\
\text{Incremental cost-efficiency of \(A/B\) = \(\frac{\text{additional cost of treatment A vs. B}}{\text{additional efficacy of treatment A vs. B.}}\) }
\]

The consumption of health resources and cost was estimated in accordance with the habitual practice in our environment (table II). It was assumed that it would be necessary to acquire a flask of every drug per month, given that the use of these drugs is not recommended after the flask has been open for some time. This also assumes that each patient would have at least two visits to the doctor in three months. An

**Table I. Joint analysis of clinical trials**

<table>
<thead>
<tr>
<th>Medication studied</th>
<th>Source of the study</th>
<th>N</th>
<th>Patient mean Age (years)</th>
<th>Base IOP (mm Hg)</th>
<th>IOP reduction after three months</th>
<th>Gave up due to related adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bimatoprost with timolole</td>
<td>Katz et al 2007 (16) and</td>
<td>533</td>
<td>62.1</td>
<td>25.9</td>
<td>35.1%</td>
<td>3.6%</td>
</tr>
<tr>
<td></td>
<td>Brandt et al 2005 (26)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Travoprost with timolole</td>
<td>Hughes et al 2005 (26)</td>
<td>151</td>
<td>64.2</td>
<td>25.3</td>
<td>34.4%</td>
<td>2.65%</td>
</tr>
<tr>
<td></td>
<td>Barney et al 2005 (27)</td>
<td>82</td>
<td>63.0</td>
<td>30.2</td>
<td>38.1%</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Schuman et al 2005 (28)</td>
<td>155</td>
<td>62.4</td>
<td>25.6</td>
<td>32.9%</td>
<td>5.2%</td>
</tr>
<tr>
<td></td>
<td>Jointly</td>
<td>388</td>
<td></td>
<td>26.5</td>
<td>34.6%</td>
<td>3.92%</td>
</tr>
<tr>
<td>Latanoprost with timolole</td>
<td>Diestelhorst et al 2006 (29)</td>
<td>255</td>
<td>61.8</td>
<td>26.0</td>
<td>35.0%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>
additional visit is also considered in the case that an adverse event took place that made a change of treatment advisable. The impact of this situation was obtained from the cases observed during the clinical trials with each drug. Finally, it was assumed that the affected patients would continue their treatment with one of the two other comparators from the second month of the model.

The consumption of health resources was evaluated in monetary terms from a social perspective. To evaluate the consumption of the drugs, the public sale price plus VAT was used, that is to say, the price at the chemists, without taking into account any type of discount for being a Social Security user. On the other hand, the cost of the medical visits was obtained from the analytical accounting of the Galician Ophthalmological Institute that was considered representative of the Spanish Public Health System.

**RESULTS**

The results obtained are summarized in table III. BT reduced the IOP by 35.1% in a period of three months; whereas, in the same period, TT and LT reduced the IOP by 34.6% and 35.0%, respectively. The average cost-efficiency ratio was estimated for BT in 5.34 € per percentage point of reduction of the IOP, for LT in 5.40 €, and for TT in 5.45 €. The incremental cost-efficacy ratio, that is to say, the additional cost for additional percentage point of reduction of IOP, was estimated by LT vs. TT at 94.65 €. The incremental cost-efficacy of BT vs. TT and of BT vs. LT resulted negative, due to the fact that, in both cases, BT was more efficient and more economical, and presented itself, as the «dominant» option.

**DISCUSSION**

Nowadays, beta-blockers and prostaglandin/prostamide analogs are first line options for the reduction of IOP in patients with POAG. The most recent clinical evidence indicates that the combined treatments of these drugs could constitute an efficient and equally secure alternative. However, complex guidelines that include the administration of various drugs could cause decreased performance of POAG, which is considered one of the main causes of failure (16). Thus, fixed combinations are a good alternative.

In an economic analysis of anti-glaucoma drugs administered in monotherapy developed in Spain, Galindo et al (17) observed, similarly to other international studies (18-22), that the beta-blocker group presented a lower hypertensor efficacy than the prostaglandin analogs, but given their low price, their average hypertensor cost-efficiency ratio (in Euros per percentage point of IOP reduction) was lower. The efficacy of our study for the combined products was above the values found by Galindo et al for the monotherapies, while our ratios of average cost-efficiency are situated among the values of Galin-
do et al for the beta-blockers and prostaglandin analogs in monotherapy. They are not comparable despite the methodologies used. This suggests that the combined products are not only the most efficient alternative, but also the most effective against the beta-blockers obtained at a cost per percentage point of IOP reduction relatively lower than the prostaglandin analogs in monotherapy.

Nevertheless, the main objective of our study was to compare the fixed combinations with prostaglandins available in Spain, and not compare the monotherapies with the combined therapies. In this way, our results indicate that, although the differences between the comparers are not very large, BT dominates TT and LT, from the pharmacological-economic point of view. That is to say, BT is presented as the most efficient and least expensive option of the three analyzed. According to a recent publication that follows a methodology coinciding with ours, the obtained results were very similar in the context of other European health systems (28).

However, it must be stated that our work has various limitations. In the first place we do not base it on a direct comparison of the efficiency of BT, TT and LT, but on a meta-analysis ad-hoc. In the absence of direct comparison clinical trials, an exhaustive revision of the literature and the indirect comparison of the alternative drugs could be a reasonable alternative. Nevertheless, it is important to highlight that the studies found that the basal values of IOP were different in the diverse groups, which does not really make the groups comparable. Another limitation is the absence of confidence intervals for the joint results, due to the difficulty of calculating these from the information revealed in the used sources. For this, we should not rule out that the differences in efficiency observed are due to luck. Nevertheless, the conclusion from an economic perspective that BT represents the best alternative of the three analyzed would not be altered in the case that its efficiency or tolerability were not statistically superior to the comparators, since it would still be the least expensive option.

Although the IOP reduction with respect to efficacy is considered as an adequate variable to evaluate the efficiency of the treatments for POAG, the relationship between the reduction of the IOP and the progress of POAG is unclear. It was not possible to evaluate the treatment efficacy in variable results, whose final aim is to preserve the patient’s quality of life (23), but, evidently, this limitation was also due to the clinical trials on which this study was based.

Finally, as in other similar studies (17,18), we have not taken into account the costs derived from the lack of efficiency beyond the temporary horizon of the utilized model (e.g., posterior surgery). Indirect costs associated to the pathology and its treatment was not even considered. It can be stated that this shortcoming introduces a bias against the most efficient treatment, but does not alter the conclusions since it similarly affects all the comparers.

In conclusion, the combination of the two first line drugs in a single presentation is efficient in the treatment of POAG and it represents a valuable treatment option that could help to improve performance. Despite our study limitations, its results indicate that of the three fixed combinations of prostaglandin/prostamide with timolole currently available on the Spanish market, BT seems to be the most economical alternative, with equal or more efficacy and tolerability.

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