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Original article

Effect on ocular blood flow of Combigan® versus placebo in patients with ocular hypertension

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A B S T R A C T

Purpose: This study was undertaken to compare the ocular haemodynamic effects of Combigan® versus placebo in patients with ocular hypertension (OHT).
Methods: Thirty patients with OHT were included in a controlled, randomised, double blind study in two parallel groups; 15 were randomised to receive Combigan® and 15 to receive placebo for a period of 3 months. At baseline and at 3 months retrobulbar blood flowmeasurements of the ophthalmic artery (OA) and central retinal artery (CRA) were taken using colour Doppler imaging(CDI) ultrasound, concurrently with intraocular pressure (IOP).
Results: Combigan® significantly reduced IOP after 3 months of treatment (P = 0.001), whereas placebo showed no significant change in IOP. The baseline haemodynamic parameters were similar between treatment and placebo groups. Patients treated with Combigan® showed a statistically significant decrease in CRA resistive index (P = 0.007).
Conclusions: Patients treated for 3 months with Combigan® showed a significant decrease of CRA resistive index that could be explained by the decrease in IOP.

Efecto de Combigan® versus placebo en el flujo sanguíneo ocular en pacientes hipertensos oculares

Palabras clave:
Ecografía doppler color
Flujo sanguíneo ocular
Combigan®
Arteria central de la retina
Arteria oftálmica
Índice de resistencia

R E S U M E N

Propósito: Estudiar los cambios hemodinámicos retrobulbares mediante ecografía doppler color, en pacientes hipertensos oculares (HTO) en tratamiento con Combigan® versus placebo.
Método: Treinta pacientes randomizados en 2 grupos paralelos fueron incluidos en un estudio prospectivo y a doble ciego; quince de ellos en tratamiento con Combigan® y quince en tratamiento con placebo, durante un periodo de 3 meses.Se obtuvieron medidas de la presión intraocular (PIO) y del flujo sanguíneo a nivel de la arteria central de la retina (ACR) y la arteria oftámica en el momento basal y a los 3 meses.

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Resultados: Combigan® redujo significativamente la PIO tras tres meses de tratamiento (p = 0,001). Los parámetros hemodinámicos basales fueron similares entre los grupos placebo y tratamiento. Los pacientes tratados con Combigan® mostraron un descenso estadísticamente significativo del índice de resistencia de la ACR (p = 0,007).

Conclusiones: Los pacientes tratados durante 3. meses con Combigan® mostraron un descenso estadísticamente significativo del índice de resistenciade la ACR que podría explicarse por el descenso de PIO.

Introduction

To date, high intraocular pressure (IOP) has been the main known risk factor for the development and progression of glaucoma. For this reason, research has been underway for many years to obtain hypotensor drugs with minimum local and systemic side effects to treat glaucoma in a safe manner.

Recent studies indicate that the instability of the optic nerve perfusion could make a bigger contribution to glaucomatous optic neuropathy than ocular blood flow reduction per se. The main cause of this instability is the alteration of self-regulation in the context of systemic vascular deregulation

The mechanisms accounting for said vascular deregulation are as of yet unknown. The existence of a possible alteration of the autonomic nervous system and the vascular endothelial cells is being discussed.[1,2]

The mechanical and vascular theories do not exclude each other, rather the contrary: deregulation would increase the susceptibility of the optic nerve to high IOP. Accordingly, new treatments must associate the ability to reduce intraocular pressure and improve ocular blood flow.

In the last decade, numerous studies have involved vascular factors in the pathogenesis and progression of glaucoma.[3-5] The prevalence of glaucoma has been indicated with small vessel diseases such as migraine, diabetes or hypertension.[6,7]

The association of glaucoma with specific circulatory events such as arterial hypotension or vessel spasms indicates that vascular factors play an important role in its pathogenesis.[8,9]

As a consequence of the above, in recent years interest in hemodynamic studies in ocular tissue has grown considerably[10-13] in an endeavor to demonstrate said deregulation and prove the optic nerve flow and neuroprotective capacity exhibited by some anti-glaucoma drugs which until then had IOP as their only target.

The final purpose of hemodynamic studies in relation to anti-glaucoma treatments is to demonstrate which of the drugs currently used in clinical practice exhibits activity at the vascular level.

Material and methods

A prospective, randomized, double-blind study with the objective of assessing retrobulbar hemodynamic changes by means of color Doppler echography (CDE), in ocular hypertensive patients (OHT) in treatment with Combigan® (eye drops in solution; Brimonidine, Timolole maleate; ALLERGAN) versus placebo. The ocular blood flow measurements were taken in the baseline visits and at treatment month 3 utilizing a Toshiba SSA-770A echograph with a 7.5MHz probe. Thirty OHT patients without previous treatment were selected in the Glaucoma Section of the Ramón y Cajal Hospital. The patients included in the study were divided randomly in 2 groups so that 15 received treatment with Combigan® and 15 with placebo for a 3-month period.

The trial was approved by the Ethical Committee of the Ramón y Cajal Hospital.

The patients excluded from the study were those who exhibited laser surgery, previous intraocular surgery or severe ocular lesions, a history of retinal vessel occlusions, visual field defects secondary to pathologies other than glaucoma, mean IOP > 30 mmHg, pre-proliferative or proliferative diabetic retinopathy, myopia >3 D, patients in treatment with betablockers, IECA and Ca antagonists.

In the first visit prior to the treatment the patients underwent an ophthalmological exploration comprising best corrected visual acuity (BCVA) in each eye, IOP by means of Goldmann applanation tonometry, biomicroscopy exploration with slit lamp, cardio frequency (CF), arterial tension (AT) and evaluation of the papilla by means of ophthalmoscopy.

The right eye of each patient was selected for the IOP and ocular blood flow measurements, even though both eyes were treated. The double-blind conditions were achieved utilizing 2 identical flasks and in both groups one drop of medication was prescribed every 12 hours.

The same ophthalmologist, with the support of an experienced echograph expert, carried out all the echographic measurements. The maximum systolic velocity (MSV) and minimum diastolic velocity (MDV) of the central retinal artery (CRA) and ophthalmic artery (OA) were taken for each patient. The resistance index (RI) was automatically calculated by the echograph. A reference angle was established in order to compare velocities for all measurements. As the RI is angle-independent due to being a quotient it was considered the most relevant parameter measured in said vessels.[14]

With the patient in supine position and eyes closed, the ultrasound transducer was applied through a thick film of conductive gel over the upper eyelid without pressing the probe over the patient's eye in order to avoid exerting a

Table 1 – Baseline characteristics of the study population

	(Combigan®) Group	Placebo group	p
BCVA	0.86 (0.11)	0.84 (0.16)	0.69
Age (years)	63.1 (9.1)	61.5 (12.3)	0.68
Sex (M/F)	9/6	6/9	
IOP (mmHg)	23.0 (1.2)	22.6 (1.8)	0.48

BCVA: best corrected visual acuity; IOP: intraocular pressure.
Mean (SD).

negative mechanical influence on the blood vessels. All the measurements were taken between 15:00 and 16:00 hours.

The OA measurements were obtained at 10-15mm of the ocular globe, nasal to the optic nerve after crossing. In the CRA, the measurements were obtained 2-3mm behind the papilla, in the anterior part of the optic nerve shadow.

The statistical study of the values obtained at baseline and after 3 months of treatment was made with the Wilcoxon test. A value of p below 0.05 was considered to be statistically significant (SPSS Inc, v15.0 Chicago).

Results

the clinical trial included 30 patients, 15 treated with Combigan® and 15 with placebo for a 3-month period. The baseline characteristics of the population for each branch of the study are summarized in table 1. No statistically significant differences were found between the control and placebo groups for these variables at baseline.

The treatment with Combigan® significantly reduced IOP (p=0.001), while the placebo group did not exhibit significant IOP changes ([p=0.33] table 2).

The ocular blood flow velocities and RI of the CRA and the OA at baseline and after treatment with Combigan® versus placebo are summarized in table 3.

Table 2 – Changes in IOP after treatment with Combigan® versus placebo in both branches of the study

	(Combigan®) Group	Placebo group	p
BCVA	0.86 (0.11)	0.84 (0.16)	0.69
Age (years)	63.1 (9.1)	61.5 (12.3)	0.68
Sex (M/F)	9/6	6/9	
IOP (mmHg)	23.0 (1.2)	22.6 (1.8)	0.48

BCVA: best corrected visual acuity; IOP: intraocular pressure.
Mean (SD).

The RI of the CRA was significantly lower than at baseline in the group treated with Combigan® (p=0.007).

Discussion

The reason why some patients with high IOP develop glaucoma while others remain indefinitely without developing said neuropathy is not clear at present. Even though IOP constitutes a clear risk factor, vascular insufficiency and deficient self-regulation of retrobulbar circulation have been considered as factors capable of playing a crucial role in the development and progression of glaucoma.[15,16] Nicolela et al[15] found that patients with open angle primary glaucoma (OAPG) exhibited lower ocular blood flow at the level of the CRA than OHT patients, suggesting that the vascular factors could be related to glaucomatous damage. According to said authors, higher ocular blood flow velocities could indicate greater vascular self-regulation capacity and therefore protect against the development of the neuropathy. Accordingly, anti-glaucomatous medication should be assessed not only for its hypotensive effect but also for its effect on retrobulbar vascularization.

The purpose of our study was to document and quantify in OHT patients the effects on ocular blood flow (CRA and OA)

Table 3 – Ocular blood flow values at baseline and after 3 months of treatment for both groups of the study

	(Combigan®) Group			Placebo group		p
BCVA	0.86 (0.11)			0.84 (0.16)		0.69
Age (years)	63.1 (9.1)			61.5 (12.3)		0.68
Sex (M/F)	9/66/9					
IOP (mmHg)	23.0 (1.2)			22.6 (1.8)		0.48
	Combigan® baseline	Combigan® 3 months	P	Placebo baseline	Placebo 3 months	P
Ophthalmic artery						
MSV (cm/s)	40.95 (16.7)	36.83 (20.2)	0.16	49.94 (17.5)	42.27 (21.1)	0.48
MDV (cm/s)	10.83 (6.9)	10.24 (10.4)	0.87	10.47 (4.7)	9.29 (5.4)	0.75
RI	0.72 (0.07)	0.69 (0.09)	0.09	0.76 (0.04)	0.76 (0.05)	0.08
Central retinal artery						
MSV (cm/s)	20.22 (5.2)	20 (5.3)	0.10	17.20 (4.7)	18.47 (6.1)	0.47
MDV (cm/s)	4.89 (1.4)	5.13 (1.7)	0.08	3.88 (1.6)	4.05 (1.7)	0.1
RI	0.74 (0.05)	0.69 (0.06)	0.007	0.75 (0.08)	0.77 (0.04)	0.62

BCVA: best corrected visual acuity; IOP: intraocular pressure.
Mean (SD).
MSV, maximum systolic velocity; MDV, minimum diastolic velocity; RI, resistance index.

of Combigan® by means of EDC. We did not assess the effect of Combigan® at the level of the posterior ciliary arteries as there are factors that suggests that the values obtained with EDC in these vessels could be hardly reproducible and therefore untrustworthy. The most relevant of these factors are, on the one hand, the short length of the vessels which makes it very difficult to apply the correction angle and on the other the broad spectrum of waves that are recorded when measuring said vessels makes their identification more difficult.

In the clinical trial, the patients treated with Combigan® experienced a statistically significant reduction of IOP (p=0.001) after 3 months of treatment, matching the results published in other studies,[16-19] whereas the placebo group did not exhibit significant IOP changes.

Numerous studies have utilized EDC to record changes at the retrobulbar level in healthy subjects and OHT and glaucomatous patients treated with topical betablockers[20-24] and brimonidine[25-29] in monotherapy, obtaining contradictory results.

Bergstrand et al[30] studied the ocular blood flow and the effect of topical treatment with timolole in OHT and OAPG patients. Said authors found that timolole 0.5% significantly diminished resistance in the OAPG group but not in the OHT group. Lachkar et al[25] assessed the effect of brimonidine in the retrobulbar blood flow of 18 OHT patients without finding hemodynamic changes with EDC.

Notwithstanding the above, there are no previous publications about ocular blood flow in OHT patients treated with Combigan®.

In our study, after 3 months of treatment with Combigan®, the RI of the CRA was significantly lower than at baseline (p=0.007). One possible explanation is that the blood flow velocity and the RI of the CRA are highly dependent on the IOP. The reduction of RI in CRA with the reduction of IOP means that vascular resistance diminishes downstream from the measuring point.[31]

The side effects registered in patients patients treated with Combigan® were similar to those published in previous papers, both in monotherapy and in fixed combination. No severe cardiopulmonary adverse effects were described.[32-35]

To conclude, EDC is a safe and noninvasive technique capable of obtaining reliable data about retrobulbar blood flow. However, trained personnel is needed to obtain reproducible data, with the limitation that it produces measurements of the ocular blood flow velocity but not of the blood flow itself. Even though the velocity in vessel having a stable diameter can be interpreted as blood flow, the EDC measurements do not provide the diameter of the vessels. An additional limitation is that it measures the vessels that supply tissue but not the flow within the retinal tissue or at the level of the ganglion retinal cells.[36] Apart from the expected IOP reduction, in this study Combigan® did not exhibit significant changes in retrobulbar hemodynamics, with the exception of our reduction in RI of the CRA (p=0.007) which could be linked to the fall in IOP.

Additional studies with larger sample sizes are necessary to establish the precise mechanism involved in the vascular response to IOP changes.

Conflict of interest

None of the authors have declared any conflict of interest.

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