CLINICAL SCIENCE

ORAL PROPRANOLOL IN VON HIPPEL LINDAU OCULAR AFFECTION

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Abstract:

Background. von Hippel Lindau (VHL) disease is a familial syndrome associated with benign and malignant tumours. These tumours appear in the retina, among other locations. The retinal hemangioblastomas are one of the earliest and most frequent manifestations of this entity, and they can lead to blindness at a young age. Propranolol could be a promising treatment for retinal hemangioblastomas in von Hippel Lindau disease

Methods. Prospective cohort study of seven patients with VHL disease and ocular affection that had rejected conventional treatment, taking oral propranolol. We evaluated them for three years, with a complete ophthalmic evaluation that included: visual acuity, intraocular pressure, an examination of the anterior segment of the eye, fundoscopy, retinography, and optical coherence tomography (OCT). Heart rate and blood pressure were also measured. During the follow-up evaluation, two patients discontinued the treatment with propranolol after the first year and rejected any further treatment for their ocular affection; the rest continued therapy.

Results. Visual acuity and tumour areas remained stable in 4 patients. Increased and new retinal exudation area was found in the two patients that discontinued the treatment with oral propranolol.

Conclusions. Oral propranolol has shown a role in the reabsorption of retinal exudates in patients with VHL affection. It could delay or stabilise the ocular disease, maintaining visual acuity and avoiding further complications in these patients. It is a well-known and available drug, without so many secondary effects, that could also have a role in other ocular diseases that course with exudation.

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Keywords. hemangioblastomas, von Hippel Lindau disease, Ophthalmology, propranolol, beta-blockers.

Introduction

von Hippel Lindau disease (OMIN 193300) is a rare pathology that affects 1/36.000 newborns. Multiple benign and malign tumours characterise the disease in different locations: retinal and central nervous system (CNS) hemangioblastomas, renal cancer, pheochromocytomas/paragangliomas, endolymphatic sac tumours, pancreatic cystadenomas and neuroendocrine tumours, cystadenomas in the epididymis and broad ligament.[1,2]
The diagnosis of this entity is established by the presence of a single typical tumour (retinal hemangioblastoma or in the central nervous system, or renal cancer) and familial VHL disease or multiple tumours, and a genetic study confirms it. The mutation in tumour suppressor gene VHL locates in chromosome 3 (3p25.3), and it is identified in these patients with an autosomal dominant inheritance pattern. Also, *de novo* mutations have been described.[1,2]

Ophthalmology clinical findings in von Hippel Lindau disease (VHL) can be characteristically found in the retina and around optic nerve head. They consist of benign tumours that are called retinal hemangioblastomas and represent the most frequent and early manifestation of the disease. They tent to appear as a solitary lesion usually located in the retinal periphery.[3-6] Other locations include juxtapapillary tumours, which arise around the optic nerve, most commonly in the temporal side.[1,3] Retinal hemangioblastomas are the most representative lesion in the eyes, derived from endothelial and glial components of the neurosensory retina and optic nerve head.[3] The anterior segment of the eye is not one of the primary affections of the disease, although it can be developed in a very severe stage of the illness secondarily. Progression and derived complications can lead to vision impairment in young patients. Screening of VHL disease should be performed when a retinal hemangioblastoma exists,[4,5] and any patient with an actual or probable diagnosis of the disease should take screening for ocular involvement.[3]

The appearance of tumours can differ depending on the stage or the location. Related to the stage, we should differentiate: *incipient tumours* that may appear as a small yellow or orange round mass located above the retina, between an arteriole and a retinal venule, or *well-established tumours,* that are a progression from the previous ones, are shown as an orange or red mass, showing tortuosity of feeder vessels (these vessels come from the optic nerve head). Related to location, we should distinguish peripheral retinal hemangioblastomas or juxtapapillary hemangioblastomas, these last ones, located immediately adjacent to the optic nerve head.[6]

Complications of this retinal tumours can be either exudative or tractional. Exudation is the most common complication. It can lead to macular oedema with intraretinal exudation (especially in juxtapapillary hemangioblastomas) or exudative retinal detachment when exudation places under retinal layers. In the tractional form, the growth of the tumour can trigger tractional retinal detachment. Fibrosis can also appear, most commonly seen as a macular pucker or macular preretinal fibrosis.[7–9] Other complications described in these patients are neovascularisation on the retina or iris (rubeosis iridis) secondary to ischemia, that can develop vitreous haemorrhage or neovascular glaucoma; cataract, or severe retinal fibrosis.[4,10,11] All of the previous events may lead to visual impairment, and that is why it is essential to the quality of life of affected patients, because most VHL patients develop retinal hemangioblastomas at a young age (22 - 40 years).[5]

Classic treatments include argon laser photocoagulation in small peripheral lesions and cryotherapy or brachytherapy in prominent lesions, or if they associate exudative retinal detachment. In small asymptomatic peripheral lesions of less than 1.5 mm that remain stable, observation is an option.[4] There is no treatment for juxtapapillary lesions since their proximity to the optic nerve can damage it, so observation is indicated in this type of tumours. Intravitreal antiVEGF injections, verteporfin photodynamic therapy and surgery (vitrectomy or excision of the tumour) have also been tried.[1,3,4,6,12–17] There is no clue of systemic non-invasive treatment that has proved beneficial on the course of ocular progression of the disease.[12]

Propranolol has also demonstrated its benefits and effects as adjuvant treatment in different kinds of cancers such as breast cancer, melanoma, liver cancer, amongst others.[18–22] It is a beta-blocker drug that has shown a proapoptotic effect by increasing BAX gene expression; antiangiogenic effect by decreasing plasma concentrations of vascular endothelial growth factor (VEGF); and a reduction in erythropoietin (EPO), Sox-2 and Oct-4, all genes involved in angiogenesis and stemness. Propranolol targets hypoxia-inducible factor (HIF) and therefore, it blocks HIF target genes. It was demonstrated in vitro on hemangioblastoma cells from CNS (that are histopathologically identical to retinal hemangioblastomas) treated with different concentrations of propranolol.[12,23,24] Propranolol also decreased VEGF in peripheral blood samples and reduced retinal exudation.[12] Our main objective is to assess long-term effect oral propranolol may have on the course of ophthalmic disease involvement.

Methods

This a prospective cohort study that took place at the Virgen de la Salud Hospital in Toledo, Spain. Ethical Committee approval was obtained before the research. Before examinations performance, all the patients signed an informed consent form for complete ophthalmic examination and secondary use of the results, data and pictures for scientific purposes.

Seven patients with ocular affection due to VHL disease were treated with oral propranolol. The lesions were peripheral or juxtapapillary retinal hemangioblastomas in one eye or both eyes. These patients had rejected more conventional treatments for their ocular disease.

We examined patients in the Ophthalmology Department. On each visit, we took the same exams: visual acuity, an examination of the anterior segment of the eye, intraocular pressure, fundoscopy, retinographies, and optical coherence tomography (OCT), and also heart rate and blood pressure, before and at the end of the study. We evaluated these patients at baseline, after a year and after three years.

We performed a visual acuity measure with a Snellen chart located 6 metres away from the patient. We used best-corrected visual acuity according to each patient's refraction. Biomicroscopic examination of the anterior segment of the eye was performed with a slit lamp from Zeiss®. We took intraocular pressure with Perkins tonometer, measured in millimetres of mercury (mm Hg) previously instillation of fluorescein and topical anaesthetic eye drops (Fluotest®, which contains: fluorescein plus oxybuprocaine). Fundus was examined under pharmacologic dilation with tropicamide and phenylephrine eye drops, to assess maximum pupil dilation and reach the most peripheral parts of the retina. Colour fundus photographs were taken with FF450 PLUS IR retinograph from Zeiss®. Optic nerve head and macular OCT were

carried out with Cirrus OCT from Zeiss®, to examine retinal nerve fibre layer in the optic nerve head and central macular thickness in the macula. We also recorded heart rate, beats per minute (bpm) and blood pressure (mmHg) during the visits.

All patients were taking oral propranolol with a dose of 120 mg per day (40 mg every 8 hours). This final dose was progressively achieved over a week. Patients did not undergo other systemic treatments of ophthalmologic interventions during these three years.

To obtain objective data of the size of tumours, we used ImageJ® software as a tool to analyse images and measure the area of each tumour at baseline and after three years.[25–27] Since this program allows area measurements, we also measured exudation areas of the retina in patients who had it. With a known measure of the image (the size of a venule, for example), and manually selecting the perimeter of the desired picture, you obtain area measurement.

Quantitative variables were expressed as means ± standard deviation (SD) and represented using a box plot diagram. We present qualitative variables as counts (n) and frequencies (%). Fit with normality was assessed using the Shapiro-Wilk test. We used Friedman's non-parametric test to evaluate the changes between the different times of the quantitative variables (visual acuity, tumour area, tumour exudation, central macular thickness and retinal nerve fibre layer). To guarantee the independence of observations (necessary hypothesis to carry out this type of contrast), comparisons of visual acuity, central macular thickness and nerve fibre layer have been carried out separately with two samples (left eyes and right eyes). A 95% confidence interval (CI) and statistical significance were considered with values less than 0.05. We carried out the analysis with SPSS 24.0 (IBM, USA).

Results

We included seven patients with VHL disease and ocular affection in our study. They were clinically evaluated in Virgen de la Salud Hospital, Toledo (Spain) and by their regular ophthalmologist, to trace the progression of the ocular condition, *see Table 1.*

They all had rejected conventional treatments because of the progression of ocular affection despite them. All the patients included had retinal peripheral or juxtapapillary hemangioblastomas due to VHL disease. Treatments that each patient underwent before this study appear in *Table 1*.

All the patients included took oral propranolol during the first year of follow up. The dosage established was 120mg/day (40mg/ 8 hours), and they did not show severe secondary effects.

During the period of evaluation, two patients discontinued the treatment (patient 3 and 4), one patient was missing (patient 6) because she had scheduled surgery for her epiretinal membrane at her hospital, and the other four patients (1,2,5,7) continued taking oral propranolol for the three years established for the study. Patient 1 decided by its own to increase the dosage until 240mg/day (80mg/8 h), after a year taking 120mg/day of propranolol, without secondary effects.

Clinical findings and characterisation of each patient. See *Table 1*.

Patient 1 had a peripheral hemangioblastoma located in the superior retina with significant exudation at baseline. It had been treated first with laser photocoagulation. After one year of taking 120 mg per day of propranolol, exudation gradually disappeared until being undetectable at control. He did not have any secondary effects due to dosage augmentation. Heart rate and blood pressure were in the normal range. His ophthalmologist treated his right eye with a new laser photocoagulation laser to prevent growth. After three years of treatment, we observed retinal fibrosis, causing traction in the retina *(Figures 1 and 2)*.

Patient 2 maintained stability. She took 120 mg per day of oral propranolol without adverse effects. No new tumours stand out or further complications during the follow-up. This patient´s last visit was done after two years.

Patient 3 had a solitary juxtapapillar hemangioblastoma in her left eye. She had retinal exudation and macular oedema that decreased after a year of oral propranolol treatment (120 mg/day). After quitting the drug, we objectified an increment of macular oedema and retinal exudation, measuring the area of retinal exudation with ImageJ® software and macular oedema with optical coherence tomography*, see Tables 2 and 3* and *Figures 1 and 2*.

Patient 4 also had a solitary juxtapapillar tumour with macular oedema, but he did not have peripheral retinal exudation. After one year of oral propranolol (120 mg/day) treatment was stopped. After three years, we observed peripheral new exudation *(see Figures 1 and 2)*.

Patient 5 had a sizeable peripheral hemangioblastoma in his right eye that had already been treated before our study with laser photocoagulation, showing dilated and tortuous feeder vessels. After one year of treatment with propranolol, no new tumours and no exudation appeared. The patient continued treatment until now (3 years). However, his ophthalmologist indicated intravitreal antiVEGF, presumably to prevent progression of the disease and right after that he suffered a retinal detachment, that is why the patient was not able to come for the last clinical assessment.

Patient 6 had a juxtapapillary hemangioblastoma and a thick epiretinal membrane. She entered the study but before a year of treatment she left because she was waiting for scheduled macular surgery to remove that epiretinal membrane.

Patient 7 had two peripheral hemangioblastomas in both eyes, small size, with no exudation or symptoms, so he had not received previous treatments. After one year of oral propranolol, ocular affection remained stable. He continued taking the drug up to three years. No new tumours appeared, and no exudation, macular oedema or other complications issued at this time.

		Baseline		After one year of oral propranolol treatment		Three years	
		RE	**LE**	**RE**	**LE**	**RE**	**LE**
Patient 1	HB	One peripheral HB in superior temporal retina, treated with laser photocoagulation before	One peripheral HB in superior temporal retina, treated with laser photocoagulation before	No new tumours	No new tumours	No new tumours Fibrosis	No new tumours
	EXUDATION	Great exudation around HB	No	No	No	No	No
Patient 2	HB	2 HB treated with laser photocoagulation	Juxtapapillar HB Epiretinal membrane	No new tumours	No new tumours	No new tumours	No new tumours
	EXUDATION	No	No	No	No	No	No
Patient 3	HB	No	Juxtapapillary HB	No new tumours	No new tumours	No new tumours	No new tumours
	EXUDATION	No	Exudation and macular oedema	No	Decreased	No	Augmented
Patient 4	HB	No	Juxtapapillary HB	No new tumours	No new tumours	No new tumours	No new tumours
	EXUDATION	No	Macular oedema	No	Decreased	No	New retinal exudation
Patient 5	HB	One peripheral HB	No	No new tumours	No new tumours	Retinal detachment	-
	EXUDATION	No	No	No	No	-	-
Patient 6	HB	No	Juxtapapillar HB, Treated previously with photodynamic therapy. Epiretinal Membrane	No	No new tumours	Withdrawal	Withdrawal
	EXUDATION	No	No	No	No	Withdrawal	Withdrawal
Patient 7	HB	Two peripheral HB	Two peripheral HB	No new tumours	No new tumours	No new tumours	No new tumours
	EXUDATION	No	No	No	No	No	No

Table 1 Clinical findings summary on each patient at different times of the study.
HB: hemangioblastoma.
RE: Right eye; LE: Left eye

Visual acuity results. Visual acuity remained stable, although the patient's three visual acuity improved after a year of drug intake, and after stopping propranolol at three years follow up, it got worst from 0,2 to 0. See *Table 2.*

		Baseline			After one year of oral propranolol treatment			Three years		
		VISUAL ACUITY	CMT (microns)	RNFL (microns)	VISUAL ACUITY	CMT (microns)	RNFL (microns)	VISUAL ACUITY	CMT (microns)	RNFL (microns)
Patient 1	RE	0,8	370	104	0,7	429	116	0,4	390	106
	LE	1	311	86	1	305	70	1	317	76
Patient 2	RE	1	291	82	1	293	83	1	294	82
	LE	0,6	337	91	0,6	329	108	0,6	319	105
Patient 3	RE	1	248	80	1	321	80	0,8	254	80
	LE	0,1	607	188	0,2	330	149	0	558	154
Patient 4	RE	1	268	97	1	261	96	1,5	263	96
	LE	0,1	939	159	0,1	1101	113	0,1	602	136
Patient 5	RE	1	301	115	1	300	117	†	†	†
	LE	1,2	278	96	1,25	269	98	†	†	†
Patient 6	RE	1	260	86	1	264	87	‡	‡	‡
	LE	0,12	188	175	0,12	668	198	‡	‡	‡
Patient 7	RE	1,25	271	99	1,25	273	100	1	289	114
	LE	1,25	271	102	1,25	285	104	1	292	112

Table 2 Baseline, one year and three years follow-up visual acuity and optical coherence tomography (OCT) measurements: central macular thickness (MCT) and retinal nerve fibre layer (RNFL). Visual acuity has no units, and its results express on a decimal scale where the minimum value is 0 and the maximum 1,5. † Patient 5 did a visit after two years, but after three years, he did not come because the patient underwent a retinal detachment after intravitreal antiVEGF injection by his usual ophthalmologist. ‡ Missing data, patient 6 withdrew the study after one year because she had a programmed surgery for epiretinal membrane by his usual ophthalmologist.
RE: Right eye; LE: Left eye

Tumour area. No significant augmentation or reduction of tumour size was objectified after one or three years follow up, and no differences between patients who were taking the drug and those who stopped it (patients 3 and 4), although we got small changes (mm^2) in our results. Measures are given in mm^2, measured with ImageJ® software at baseline and after three years. Patient 1 tumour was not possible to estimate because he had it treated with laser photocoagulation with scarring at baseline; he developed severe fibrosis after three years, so it was not possible to determine whether the tumour starts and ends. No new tumours appeared during the clinical fundus examination. We monitored existent hemangioblastomas along with the study. See *Table 3* for results.

Exudation area: patient 1, who had the most significant area of retinal exudation before propranolol treatment started, showed the most spectacular reabsorption of exudation, and it maintained after three years of propranolol intake (*Figure 1*). Patient 3 retinal exudation reduced after a year of treatment, but it increased after three years without treatment. Patient 4 who did not have retinal exudation at baseline, and after a year of therapy, developed it after three years follow up, he also stopped drug intake after one year (*Figure 1*). The exudation area measured with ImageJ® software presents in mm^2. Results appear in *Table 3*.

Central macular thickness (CMT) and retinal nerve fibre layer (RNFL): no relevant variations show up in the retinal fibre layer measured with optical coherence tomography. Regarding central macular thickness, the patient's 3 CMT decreased after a year of treatment and augmented after she stopped treatment at three years follow-up. It relates to macular oedema. The patient's 6 CMT increased despite therapy due to the progression of a previous existent macular epiretinal membrane that thickened retinal layers. The patient's 4 CMT did not improve after a year of treatment, but it decreased after three years, although he stopped treatment (*Figure 2*). Measures present in microns, made with Zeiss® Cirrus Optical coherence tomography (OCT).

		Basal tumour area (mm^2)	**Basal retinal exudation (mm^2)**	**Tumour area after one year (mm^2)**	**Retinal exudation after one year (mm^2)**	**Tumour area after three years (mm^2)**	**Retinal exudation after three years (mm^2)**
Patient 1	RE	-	0.2895	-	0	-	0
	LE	-	-	-	-	-	-
Patient 2	RE	-	-	-	-	-	-
	LE	3.029	-	2.767	-	3.721	-
Patient 3	RE	-	-	-	-	-	-
	LE	3.951	0.0049336	2.582	0.0020904	2.785	0.0191141
Patient 4	RE	-	-	-	-	-	-
	LE	7.117	0	7.923	0	9.026	0.01
Patient 5	RE	5.531	-	7.488	-	7.471†	-
	LE	-	-	-	-	-	-
Patient 6	RE	-	-	-	-	-	-
	LE	3.944	-	3.868	-	-	-
Patient 7‡	RE	3.323	-	3.269	-	4.126	-
		0.602	-	0.632	-	0.604	-
	LE	3.131	-	3.169	-	3.568	-
		1.06	-	1.336	-	2.692	-

Table 3 **Tumour and retinal exudation area measurement.** †The patient's 5 last visit took place after two years. The patient underwent a retinal detachment after intravitreal antiVEGF injection by his ophthalmologist and did not come at the third-year visit. ‡ Patient 7 presents two hemangioblastomas on each eye.
mm^2: square millimetres.
RE: Right eye; LE: Left eye

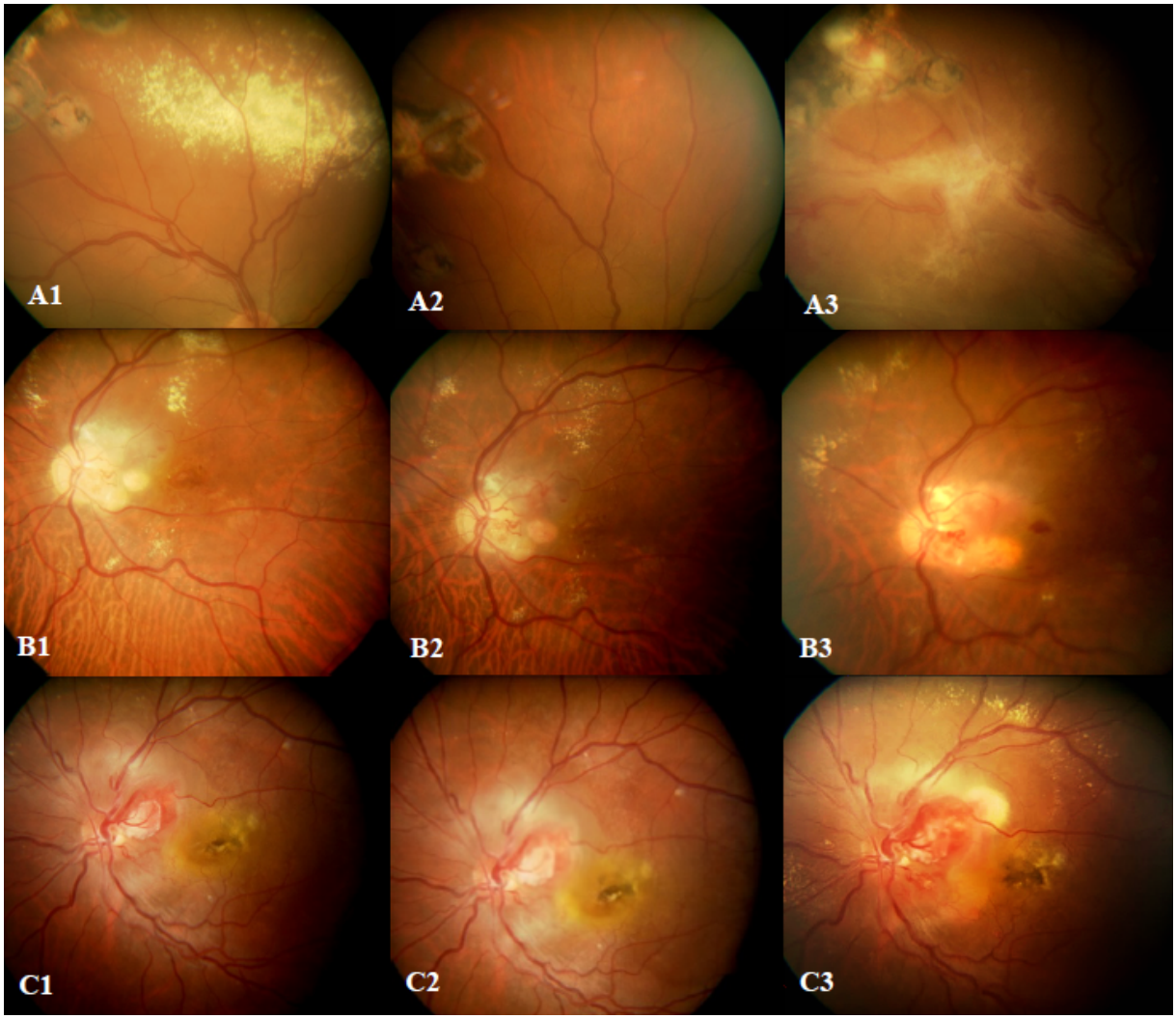

Figure 1 Fundus retinographies of patients with retinal exudation. *Patient 1 is showed like A; Patient 3 like B; Patient 4 like C; Number 1= Baseline; 2= After one year; 3= After three years*. Patient 1 presents abundant retinal exudation at baseline (A1), after one year of oral propranolol treatment, exudation gradually disappeared completely (A2). After three years of treatment (A3), no retinal exudation is present, but preretinal striking fibrosis causing retinal traction highlights, this could be due to laser (performed after a year by his regular ophthalmologist) or the natural progression of the disease rather than oral medication. Patient 3 presents retinal exudation, macular oedema and a congested juxtapapillary hemangioblastoma before any treatment was introduced (B1). After one year of oral propranolol intake, a reduction of retinal exudation and tumour congestion emerges in image B2. After being three years without treatment: tumour appears congestive a little bit larger with an adjacent haemorrhage, and also, retinal exudation is augmented (B3). Patient 4 has juxtapapillary hemangioblastoma con chronic macular oedema at baseline (C1). After a year of oral propranolol treatment, the tumour seems a little bit more congested than before (C2). After three years without any treatment, the tumour appears larger, significantly more congestive, and new retinal exudation has appeared (C3).

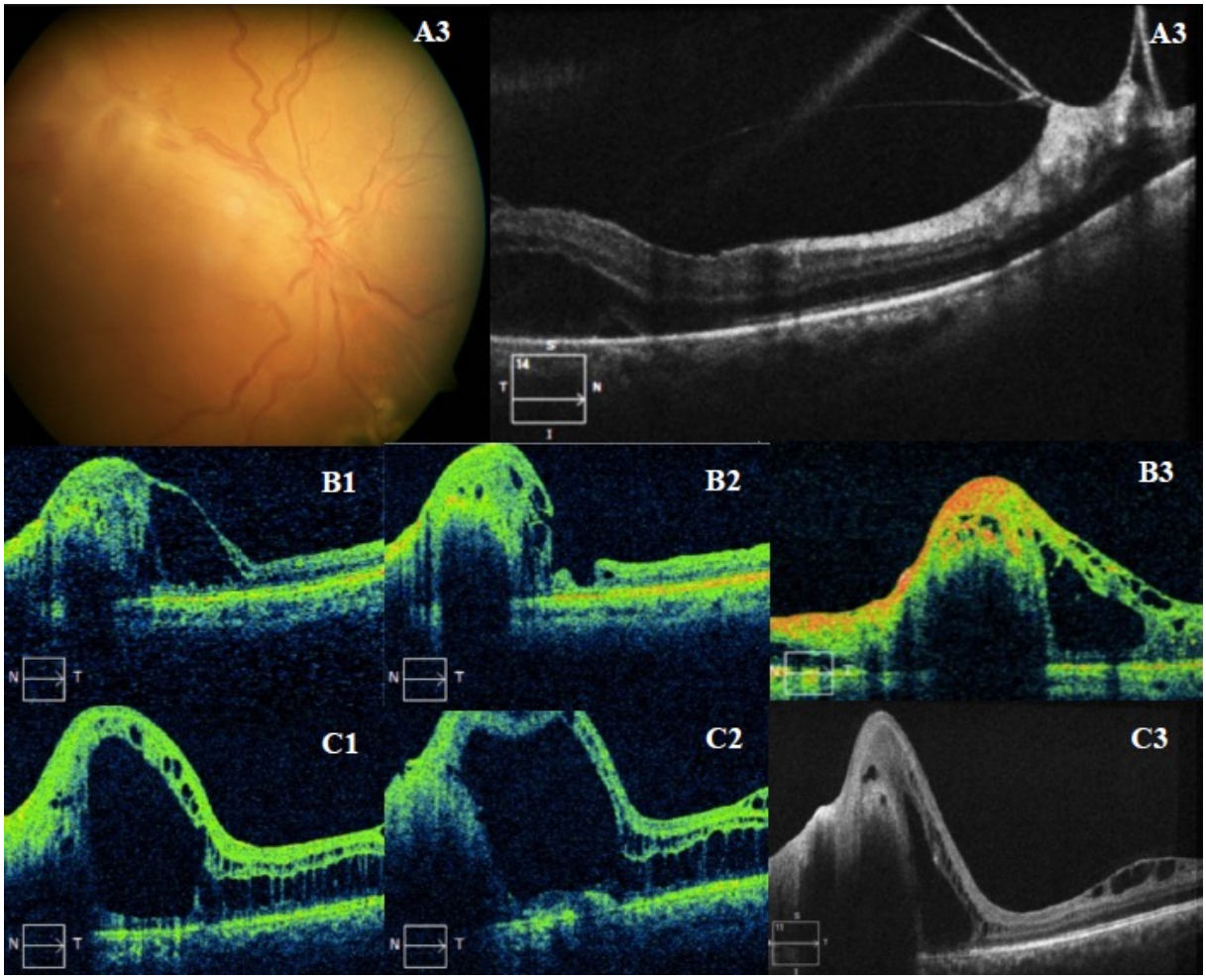

Figure 2 OCT findings in patients with retinal exudation. *Patient 1 is showed like A; Patient 3 described like B; Patient 4 like C; 1= Baseline; 2= After one year; 3= After three years*. Patient 1 developed preretinal fibrosis with traction at the time of the 3-years follow-up, in the right picture we can see a high definition OCT of it (A3). Patient´s 3 OCT looks improved after a year of oral treatment showing less macular exudation (B2), despite it increased three years after she suspended oral treatment (B3). Although macular oedema was reduced at the time of 3 years follow up in patient 4, tumour size and peripheral retinal exudation both increased (C3).

Regarding oral propranolol after three years of treatment, no noticeable or adverse events were found in terms of blood pressure and heart rate, both of them are into the normal range. We overlooked relevant findings in terms of intraocular pressure, before and at the end of the study. See *Tables 4 and 5*. Data from patient 5 is missing because he had a retinal detachment and could not come for an assessment. Patient 6 withdrew the study to take a scheduled epiretinal membrane surgery at her hospital.

	HEART RATE (bpm)		BLOOD PRESSURE (mmHg)	
	BASELINE	3 YEARS	BASELINE	3 YEARS
Patient 1	64	62	144/90	120/80
Patient 2	87	85	120/76	111/65
Patient 3	60	82	140/80	140/80
Patient 4	94	74	130/80	130/70
Patient 5	74	-	120/60	-
Patient 6	89	-	110/80	-
Patient 7	86	61	120/70	110/60

Table 4 Heart rate and blood pressure recordings at baseline and after three years.
bpm: beats per minute; mmHg: millimetres of mercury.

	INTRAOCULAR PRESSURE (IOP) mmHg			
	BASELINE		3 YEARS	
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE
Patient 1	11	12	10	12
Patient 2	10	10	14	14
Patient 3	14	18	17	19
Patient 4	14	13	10	14
Patient 5	14	13	-	-
Patient 6	12	16	-	-
Patient 7	15	16	16	17

Table 5 Intraocular pressure measured in mmHg before and after three years.
IOP: intraocular pressure. mmHg: millimetres of mercury.

After comparing the evolution of the variables over three years regarding visual acuity, central macular thickness, retinal nerve fibre layer, and exudation area, no statistically significant results show up, (p value>0.05) see *Table 6* and *Figure 3*. In terms of visual acuity, no changes mean this variable is stable, which is good because it reflects eye function and it has to be maintained. The same happens with CMT, RNFL and tumour area since no significant changes or growth show up. The exudation area is not statistically significative, since the sample size is reduced (three patients out of seven with exudation), but clinically it represents a relevant finding.

	Baseline	**1 Year**	**3 Years**	**p value***
VA (N=12)	0,82 ± 0,41	0,82 ± 0,41	0,74 ± 0,46	0.091
CMT (N=14)	352,86 ± 194,14	387,71 ± 230,87	370,63 ± 136,24	0.607
RNFL (N=14)	111,43 ± 35,61	108,5 ± 32,30	109,25 ± 26,45	0.495
TA (N=9)	3,46 ± 2,14	3,64 ± 2,66	4,25 ± 2,72	0.072
TE (N=7)	0,04 ± 0,11	0,0003 ± 0,0007	0,00416 ± 0,0076	0.272

Table 6 Statistical means of different variables at baseline, after 1 and 3 years. VA: visual acuity; CMT: central macular thickness; RNFL: retinal nerve fibre layer (N=14); TA: tumour area; TE: tumour exudation. N: sample size. Mean ± Standard deviation issue in the table.
***Friedman Test

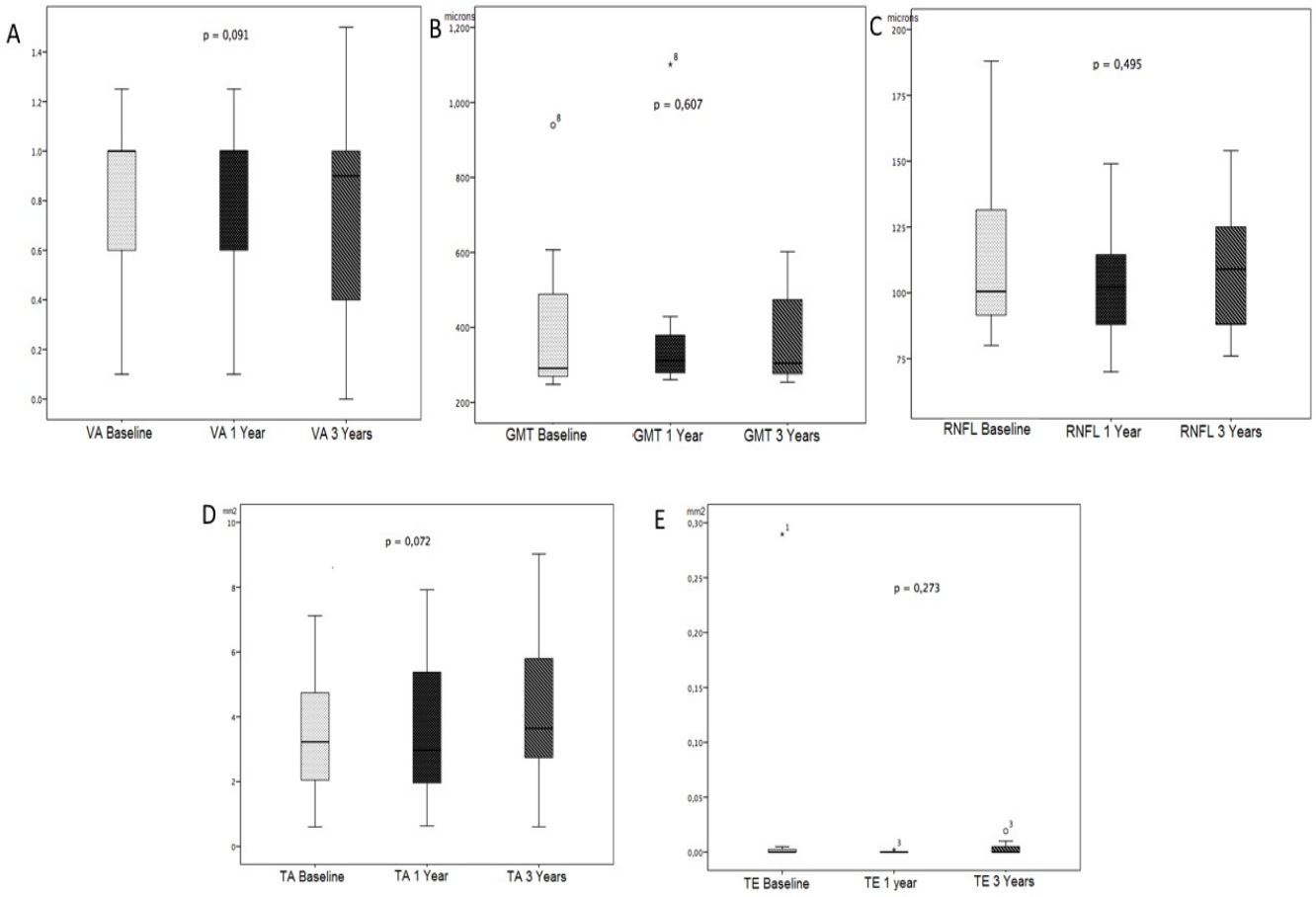

Figure 3 Blox pot diagram (median, upper quartile, lower quartile, upper extreme, lower extreme, whisker and single data point) showing the values of the following parameters at the baseline, at the year and the three years of monitoring.
A. VA: visual acuity, **B**. CMT: central macular thickness (microns), **C**. RNFL: retinal nerve fibre layer (microns), **D**. TA: tumour area (mm^2), **E**. TE: tumour exudation (mm^2).
*p= Friedman Test

Discussion

Ocular affection in VHL disease usually affects young patients at a mean age of 25 years old, and most of them are between 10 to 40 years old.[28–30] The complications derived from it can cause them blindness, that is why it is crucial to find new strategies for their treatment to prevent the evolution of their ocular affection.[28,31]

Propranolol is a beta-blocker drug that has shown antiangiogenic properties such as control of endothelial proliferation, antiapoptotic, inhibition of tumour cells and also vasoconstriction properties.[23,24,32–34] It revealed successful results in other vascular diseases like hemangiomas.[35–39] No other systemic treatment is described until now for ocular affection in VHL disease. Propranolol could prevent tumour growth and some of the complications, like exudation or macular oedema that could lead these patients to different grades of visual impairment.[12]

In our study, we observed that visual acuity remained stable in the patients who took oral propranolol (120-240 mg/day). We did not found differences during the follow up in the third year, although four of the patients that were monitored continued treatment after the first year. We should remark that maintaining visual acuity stability is very important to give these patients a better quality of life, and none of them aggravated with this treatment. It is well-known that juxtapapillary tumours are related to worst visual acuity since there is no treatment available for them due to its proximity to the optic nerve head and macula. Until now, the treatment for them is only to observe because doing anything invasive can damage these critical structures and produce more harm to these patients[3], permanent scotoma, and poor visual outcomes originate after laser photocoagulation of juxtapapillary lesions.[40]

Concerning the tumour area, it also remained stable for the three years of study. We did not find new tumours grew up after the third year of following up in our patients. As far as we know,[30] the natural progression of the tumours could be stability, spontaneous growth or regression.[3] Those that show progression have a higher risk of producing earlier complications. Some authors have published that the probability of new lesions is not constant in all patients.[3]

Respect to the exudation area, our patients showed regression of exudation after the first year of treatment with oral propranolol. We should focus on this point because, the two patients who discontinued the treatment after the first year, showed an increment of retinal exudation objectively measured with ImageJ® software. Although these changes were not statistically significant at the end of the third year, there is a clinical relevance for these findings, since the introduction of the drug correlates with an improvement or disappearance of exudates. Conversely, suspension of the medicine seems to worsen exudation of the retina in our patients.

About Central Macular Thickness (CMT) and Retinal Nerve Fibre Layer (RNFL), we observed that peripheral tumours produced less affection of macular structure than those who had juxtapapillary tumours, and it can be explained by the proximity of the tumour to the macula.[1-3]

Related to the safety of the treatment employed, we had evaluated the possible secondary effects in the patients. Dosage of 120mg/day until 240mg/ day did not produce significant changes in heart rate or blood pressure measurements in our patients. The recommended dose of propranolol for infantile hemangiomas is 2 to 3 mg/kg/day, and it seems that higher amounts up to 3 to 4.5 mg/kg/day are not more effective than conventional ones.[39] The optimum dosage of the drug remains unclear. Although different authors tried high doses of propranolol (4.5 mg/kg/day) it seems that dosage does not affect the rate of therapeutic efficiency regarding hemangiomas[39] and low doses (1-1.5 mg/kg/day) are efficacious; lesions which do not show an initial response to the lower dose are unlikely to respond to the higher dose quantity of 3-4 mg/kg/day, so non-responsive patients to the treatment remain.[34] In infantile hemangiomas, after initial regression, the later improvement is much slower, sometimes with periods of stagnation, and they recommend treatment should be continued for at least six months because early cessation can cause a relapse,[34,41] which we found in the patients that discontinued treatment. The maximum dosages of propranolol should be adjusted individually to each patient depending on the response and tolerability, but depending on the affection in which it is used the following doses have demonstrated to be safe: 640 mg/day in hypertension, 480mg/day in angina, 240 mg/day in migraine and tachycardia, 160mg/day in arrhythmias, hyperthyroidism and hypertrophic obstructive cardiomyopathy, and up to 160mg/12 hours in upper

gastrointestinal bleeding. In elderly patients, it may be necessary to initiate treatment with lower doses than those in young patients, also considering renal and liver function.[42]

Limitations of the study: Since von Hippel Lindau is a rare disease and we are trying a new treatment, consequently our sample size is small. Regarding treatment, one patient withdrew the research to attend a scheduled surgery, another one could not come for the last visit of the study due to retinal detachment and two patients decided to stop treatment after one year. All of this can partially modify results obtained in the third year follow up, but it also has the advantage to show a worsening of exudation without propranolol treatment. Further long-term studies would be necessary about this drug in von Hippel Lindau disease. There is also a lack of previous studies on this topic.

Conclusions

Propranolol is the first oral systemic treatment that has been tried in ocular disease in patients with von Hippel Lindau until now. It could be helpful by controlling the growth of retinal hemangioblastomas and preventing and reverting retinal exudation due to its proapoptotic and antiangiogenic properties. We would focus on the importance of regression or stability of exudation that had the patients who maintained the treatment for the three years because of the treatment limitations that the ocular affection has in these kinds of patients (more, in those who had juxtapapillary tumour due to its closure to the macula and higher risk of harm). It may be helpful as a new weapon for ocular exudation in von Hippel Lindau, alone or coadjuvant to other treatment options. This treatment could be useful also in other ocular diseases that involve retinal exudation. More studies will be needed for this topic in the future.

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List of abbreviations

bpm: beats per minute; **CMT:** central macular thickness; **CNS:** Central nervous system; **CI:** confidence interval; **EPO:** erythropoietin; **HB:** hemangioblastoma; **HIF:** Hypoxia-inducible factor; **IOP:** intraocular pressure; **mm^2:** square millimetres; **mmHg:** millimetres of mercury; **OCT:** optical coherence tomography; **RNFL:** retinal nerve fibre layer; **SD:** standard deviation; **VHL:** von Hippel Lindau; **VEGF:** Vascular endothelial growth factor.

Declarations

Ethics approval and consent to participate and consent for publication. Ethical Committee approval was obtained before the research. Before examinations performance, all the patients signed an informed consent form for complete ophthalmic examination and secondary use of the results, data and pictures for scientific purposes.

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