Oral Propranolol in Von Hippel Lindau Ocular Affection

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Abstract:

Purpose. von Hippel Lindau (VHL) disease is a familiar syndrome associated with benign and malignant tumors. These tumors appear in the retina, cerebellum, spinal cord, and kidney. 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. Seven patients with VHL disease and ocular affection that had rejected conventional treatment were included. Prospective analysis of seven patients was performed. 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 on each patient 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 for the three years.

Results: Visual acuity and tumor 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 von Hippel Lindau affection. It could delay or stabilize 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.

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 tumors characterize the disease in different locations: retinal and central nervous system (CNS) hemangioblastomas, renal cancer, pheochromocytomas/paragangliomas, endolymphatic sac tumors, pancreatic cystadenomas and neuroendocrine tumors, cystadenomas in the epididymis and broad ligament.^{1,2}

The diagnosis of this entity is established by the presence of a single typical tumor (retinal hemangioblastoma or in the central nervous system, or renal cancer) and familiar VHL disease, or multiple tumors, and it is confirmed by genetic study. The mutation in tumor 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 or on the optic nerve head. They consist in benign tumors that are called retinal hemangioblastomas, and represent the most frequent and early manifestation of the disease. They tend to appear as a solitary lesion usually located in the retinal periphery.³⁻⁶ Other locations include juxtapapillary tumors, 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 or juxtapapillary 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 tumors can differ depending on the stage or the location. Related to the stage, we should differentiate: *incipient tumors* 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 tumors*, 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, this last ones, located immediately adjacent to the optic nerve head.⁶

Complications of this retinal tumors can be either exudative or tractional. Exudation is the most common complication. It can lead to macular edema with intraretinal exudation (especially in juxtapapillary hemangioblastomas) or exudative retinal detachment when exudation places under retinal layers. Tractional form 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 neovascularization on the retina or iris (rubeosis iridis), that can develop vitreous hemorrhage 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 significant 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 tumors. Intravitreal antiVEGF injections, verteporfin photodynamic therapy and surgery (vitrectomy or excision of the tumor) 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)^{12,23,24} treated with different concentrations of propranolol.^{13,24,25} 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.

Materials and methods

This a prospective cohort study that took place at Virgen de la Salud Hospital, 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, all of them original from Spain, 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 at the Ophthalmology Department in Virgen de la Salud Hospital, Toledo, Spain. 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 meters 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 millimeters of mercury (mm Hg) previously instillation of fluorescein and topical anesthetic 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. Color 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 fiber 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 tumors, we used ImageJ® software as a tool to analyze images and measure the area of each tumor 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 $\pm$ 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, tumor area, tumor exudation, central macular thickness and retinal nerve fiber 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 fiber 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 in 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 characterization 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 edema that decreased after a year of oral propranolol treatment (120 mg/day). After quitting the drug, we objectified an increment of macular edema and retinal exudation, measuring the area of retinal exudation with ImageJ® software and macular edema with optical coherence tomography, *see Tables 2 and 3 and Figures 1 and 2*.

Patient 4 also had a solitary juxtapapillar tumour with macular edema, 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 edema or other complications issued at this time.

Visual acuity results. Visual acuity remained stable, although the patient's 3 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*.

Tumor area. No significant augmentation or reduction of tumor 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 (mm²) in our results. Measures are given in mm², measured with ImageJ® software at baseline and after three years. Patient 1 tumor 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 tumor starts and ends. No new tumors 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 mm². Results appear in *Table 3*.

Central macular thickness (CMT) and retinal nerve fiber layer (RNFL): no relevant variations show up in the retinal fiber 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 edema. 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).

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.

After comparing the evolution of the variables over three years regarding visual acuity, central macular thickness, retinal nerve fiber 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 tumor 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.

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's 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, proapoptotic, inhibition of tumour cells and also vasoconstriction properties.^{23,24,32-34} It revealed successful results in other vascular diseases like hemangiomas.³⁵⁻³⁹ Propranolol could prevent tumour growth and some of the complications, like exudation or macular edema 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 find 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 patients³, 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.²⁹ 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 hemangiomas³⁹ 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,^{34,40} which we found in the patients that discontinued the 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, 480 mg/day in angina, 240 mg/day in migraine and tachycardia, 160 mg/day in arrhythmias, hyperthyroidism and hypertrophic obstructive cardiomyopathy, and up to 160 mg/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.

Limitations of the study. Our sample is small because of von Hippel Lindau is a rare disease and the ocular affection takes care during the middle age. Respect to the 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 the first year. All of these things can partially modify results obtained after the third year of follow up, but also show us a worsening of exudation in the patients that discontinued the treatment with oral propranolol. There are not published other studies on this topic.

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 this kind 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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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.

Availability of data and materials. Not applicable for this article.

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References

1. Wong WT, Agrón E, Coleman HR, Tran T, Reed GF, Csaky K, et al. Clinical characterization of retinal capillary hemangioblastomas in a large population of patients with von Hippel-Lindau disease. *Ophthalmology*. 2007/06/01 ed. 2008 Jan;115(1):181–8.
2. Chittiboina P LRR. Von Hippel-Lindau disease. *Handb Clin Neurol*. 2015;132:139–56.
3. Karimi S, Arabi A, Shahraki T, Safi S. von Hippel-Lindau Disease and the Eye. *Journal of ophthalmic & vision research*. 2020;15(1):78–94.
4. Ruppert MD, Gavin M, Mitchell KT, Peiris AN. Ocular Manifestations of von Hippel-Lindau Disease. *Cureus*. 2019 Aug;11(8): e5319.
5. Binderup MLM, Stendell A-S, Galanakis M, Møller HU, Kiilgaard JF, Bisgaard ML. Retinal hemangioblastoma: prevalence, incidence and frequency of underlying von Hippel-Lindau disease. *The British journal of ophthalmology*. 2018 Jul;102(7):942–7.
6. Salmon J. Kanski's Clinical Ophthalmology: A Systematic Approach. 9th Editio. Elsevier; 2019.
7. Vortmeyer AO, Chan CC, Chew EY, Matteson DM, Shen DF, Wellmann A, et al. Morphologic and genetic analysis of retinal angioma associated with massive gliosis in a patient with von Hippel-Lindau disease. *Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie*. 1999 Jun;237(6):513–7.
8. Laatikainen L, Immonen I, Summanen P. Peripheral retinal angiomalike lesion and macular pucker. *American journal of ophthalmology*. 1989 Nov;108(5):563–6.
9. Singh AD, Shields CL, Shields JA. MAJOR REVIEW von Hippel – Lindau Disease. 2001;46(2).
10. Venkatesh P, Takkar B. Proposed Classification System for Retinal Capillary Angiomatosis. Vol. 61, *Ophthalmic research*. Switzerland; 2019. p. 115–9.

11. Pulido JS, Dalvin LA, Olsen TW, Mano F, Yu M, Shields CL. Peripheral retinal nonperfusion using widefield imaging with von Hippel - Lindau disease. *International Journal of Retina and Vitreous*. 2018;1–3.
12. González-Rodríguez B, Villar K, De G, Aguirre DT, Rodríguez-padial L, Albiñana V, et al. Evaluation of the safety and effectiveness of oral propranolol in patients with von Hippel-Lindau disease and retinal hemangioblastomas: phase III clinical trial. *BMJ Open Ophthalmology*. 2019;1–6.
13. Karimi S, Nikkhah H, Ahmadi H, Safi S. Intravitreal injection of propranolol for the treatment of retinal capillary hemangioma in a case of von Hippel-Lindau. *Retinal cases & brief reports*. Retin Cases Brief Rep. 2020 Fall;14(4):305-309
14. VAIL D. Angiomatosis retinae, eleven years after diathermy coagulation. *Transactions of the American Ophthalmological Society*. 55:217–8.
15. Sturzeneker G, Maia A, Morales M, N Belfort R. Vitreoretinal Surgery and Panretinal Photocoagulation in a Patient with Multiple Large Retinal Capillary Hemangiomas (von Hippel-Lindau Disease): A Novel Approach. Vol. 10, *Case reports in ophthalmology*. Switzerland; 2019. p. 327–33.
16. Wong WT, Liang K, Hammel K, Coleman HR, Chew EY. Intravitreal ranibizumab therapy for retinal capillary hemangioblastoma related to von Hippel-Lindau disease. 2011;115(11):1957–64.
17. Lazzeri S, Figus M, Di Bartolo E, Rizzo S, Nardi M. Verteporfin photodynamic therapy for retinal hemangioblastoma associated with Von Hippel-Lindau disease in a 9-year-old child. Vol. 39, *Clinical & experimental ophthalmology*. Australia; 2011. p. 179–81.
18. Cole SW, Sood AK. Molecular pathways: Beta-adrenergic signaling in cancer. *Clinical Cancer Research*. 2012 Mar;18(5):1201–6.
19. Phadke S, Clamon G. Critical Reviews in Oncology / Hematology Beta blockade as adjunctive breast cancer therapy: A review. *Critical Reviews in Oncology / Hematology*. 2019;138(October 2018):173–7.
20. Pasquier E, Ciccolini J, Carre M, Giacometti S, Fanciullino R, Pouchy C, et al. Propranolol potentiates the anti-angiogenic effects and anti-tumor efficacy of chemotherapy agents: implication in breast cancer treatment. *Oncotarget*. 2011;2(10):797.
21. Wang F, Liu H, Wang F, Xu R, Wang P, Tang F, et al. Propranolol suppresses the proliferation and induces the apoptosis of liver cancer cells. *Molecular medicine reports*. 2018 Apr;17(4):5213–21.
22. De Giorgi V, Grazzini M, Benemei S, Marchionni N, Botteri E, Pennacchioli E, et al. Propranolol for off-label treatment of patients with melanoma: results from a cohort study. *JAMA oncology*. 2018;4(2):e172908–e172908.

23. Albiñana V, María R, Escribano J, Soler I, Padial LR, Recio-poveda L, et al. Repurposing propranolol as a drug for the treatment of retinal haemangioblastomas in von Hippel-Lindau disease. 2017;1–10.
24. Albiñana V, Villar K, De G, Serrano-heras G, Segura T, Perona-moratalla AB, et al. Propranolol reduces viability and induces apoptosis in hemangioblastoma cells from von Hippel-Lindau patients. Orphanet Journal of Rare Diseases. 2015;1–12.
25. Schneider CA, Rasband WS, Eliceiri KW. NIH Image to ImageJ: 25 years of image analysis. Nature methods. 2012 Jul;9(7):671–5.
26. Schindelin J, Rueden CT, Hiner MC, Eliceiri KW. The ImageJ ecosystem: An open platform for biomedical image analysis. Molecular reproduction and development. 2015;82(7–8):518–29.
27. Dominguez VM, Agnew AM. The use of ROI overlays and a semi-automated method for measuring cortical area in ImageJ for histological analysis. American journal of physical anthropology. 2019 Feb;168(2):378–82.
28. Aronow ME, Wiley HE, Gaudric A, Krivosic V, Gorin MB, Shields CL, et al. VON HIPPEL–LINDAU DISEASE: Update on Pathogenesis and Systemic Aspects. RETINA. 2019;39(12).
29. Maher ER, Yates JR, Harries R, Benjamin C, Harris R, Moore AT, et al. Clinical features and natural history of von Hippel-Lindau disease. The Quarterly journal of medicine. 1990 Nov;77(283):1151–63.
30. Chang JH, Spraul CW, Lynn ML, Drack A, Grossniklaus HE. The two-stage mutation model in retinal hemangioblastoma. Ophthalmic genetics. 1998 Sep;19(3):123–30.
31. Toy BC, Agron E, Nigam D, Chew EY, Wong WT. Longitudinal analysis of retinal hemangioblastomatosis and visual function in ocular von Hippel-Lindau disease. Ophthalmology. 2012 Dec;119(12):2622–30.
32. Rauski A, Kosec D, Vidic-Dankovic B, Plecas-Solarovic B, Leposavic G. Effects of beta-adrenoceptor blockade on the phenotypic characteristics of thymocytes and peripheral blood lymphocytes. The International journal of neuroscience. 2003 Dec;113(12):1653–73.
33. Ji Y, Chen S, Xu C, Li L, Xiang B. The use of propranolol in the treatment of infantile haemangiomas: an update on potential mechanisms of action. The British journal of dermatology. 2015 Jan;172(1):24–32.
34. Prasad A, Sinha AK, Kumar B, Prasad A, Kumari M. Individualized dosing of oral propranolol for treatment of infantile hemangioma: a prospective study. The Pan African medical journal. 2019;32:155.
35. Léauté-Labrèze C, Harper JJ, Hoeger PH. Infantile haemangioma. Lancet (London, England). 2017 Jul;390(10089):85–94.

36. Lin Z, Wang L, Huang G, Wang W, Lin H. Propranolol inhibits the activity of PI3K, AKT, and HIF-1alpha in infantile hemangiomas. *Pediatric surgery international*. 2018 Nov;34(11):1233–8.
37. Darrow DH. Management of Infantile Hemangiomas of the Airway. *Otolaryngologic clinics of North America*. 2018 Feb;51(1):133–46.
38. Laken PA. Infantile Hemangiomas: Pathogenesis and Review of Propranolol Use. *Advances in neonatal care: official journal of the National Association of Neonatal Nurses*. 2016 Apr;16(2):135–42.
39. Wu W, Wang H, Hao J, Gao Z, Li F, Chen Y. Therapeutic efficacy of propranolol for infantile hemangiomas. *Oral surgery, oral medicine, oral pathology and oral radiology*. 2019 Aug;128(2):132–8.
40. Katona G, Csákányi Z, Gács E, Szalai Z, Ráth G, Gerlinger I. Propranolol for infantile haemangioma: striking effect in the first weeks. *International journal of pediatric otorhinolaryngology*. 2012;76(12):1746—1750.

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; **mm²:** square millimeters; **mmHg:** millimeters of mercury; **OCT:** optical coherence tomography; **RNFL:** retinal nerve fiber layer; **SD:** standard deviation; **VHL:** von Hippel Lindau; **VEGF:** Vascular endothelial growth factor.

Figures

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).

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 (mm²), E. TE: tumour exudation (mm²). *p= Friedman Test