**Title:** Intravitreal metoprolol injections: Is it a safe option for choroidal hemangioma?

**Authors:** Leandro Chaves MD1, André Messias MD, PhD.1, Rodrigo Jorge MD, PhD.1

**Institution:**1Department of Ophthalmology, Ribeirão Preto School of Medicine, University of São Paulo, Ribeirão Preto, Brazil

L. Chaves and R.Jorge are the primary contributors to research design. R. Jorge, L. Chaves, and A. Messias are responsible for research execution and data acquisition. All authors were primary contributors to data analysis and interpretation. Manuscript was prepared by R. Jorge, L. Chaves, and A. Messias with final revisions and approval provided by all authors.

**Corresponding Author:**

Rodrigo Jorge, M.D., Ph.D.

Department of Ophthalmology, Ribeirão Preto School of Medicine, University of São Paulo Ribeirão Preto

3900, Bandeirantes Avenue, Ribeirão Preto, SP 14049-900, Brazil

Tel./Fax: 55 (16) 3602-2860

Email: retinausp@gmail.com

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**Title:** Intravitreal metoprolol injections: Is it a safe option for choroidal hemangioma? **Purpose:** To evaluate the ocular toxicity of intravitreal metoprolol injections in five eyes with circumscribed choroidal hemangioma. **Methods:** Five eyes of five subjects diagnosed with circumscribed choroidal hemangioma and unsuccessfully treated with intravitreal anti‐VEGF agents were enrolled and received off label intravitreal injections of metoprolol (50µg/0.05 ml). Basal and follow-up tests included best-corrected visual acuity, intraocular pressure assessment, anterior chamber cellular score/flare, vitreitis classification, retinography, fundus autofluorescence, and ISCEV full-field scotopic and photopic standard protocols. The follow-up period was 30 days, and the results of the tests were compared using a paired t-test: pre vs. post-treatment.

**Results:** There were no significant changes in visual acuity, tonometry, retinography and fundus autofluorescence. The subretinal and/or intraretinal fluid improved in three patients four weeks after the metoprolol injection. There was no significant difference in all ISCEV recommended ERG parameters regarding a- and b-wave amplitude and implicit time, and oscillatory potentials maximal amplitude. No subject developed any clinical sign of intraocular inflammation. **Conclusion:** No signs of acute ocular toxicity of 50µg/0.05ml intravitreal metoprolol injections in patients with circumscribed choroidal hemangioma were identified. Long term retinal toxicity, different concentrations, drug resistance and complications form repeated-intravitreal injections were not accessed. The off‐label use of intravitreal metoprolol tartrate (50 mcg/0,05ml) may be of interest to possible new therapeutic approaches.

**Introduction**

The beta-adrenergic system has been investigated as a possible target for pharmacologic treatment in neovascular retinal diseases1. It is likely to be involved both in angiogenic response and neural damage. Recently the off-label use of intraocular beta-blockers associated with anti-VEGF agents is under investigation for wet age-related macular degeneration2 and the use of these drugs was related on the literature with positive results in a case of retinal capillary hemangioma3 and another of circumscribed choroidal hemangioma4. Although the majority of published data regards the use of propranolol, a nonspecific b–adrenergic receptor antagonist, its intravenous preparation is not widely available in some countries.

Intravenous metoprolol tartrate is a ß1-selective adrenergic blocker with interesting physical-chemical characteristics for intraocular use. The low molecular weight (684.82 g/mol) might allow it to penetrate the retina into the subretinal space and choroid easily and its pH of 6.8 and osmolarity of 296 mOSm/Kg are comparable with others intraocular drugs5. *In vitro* studies, metoprolol tartrate has proven to be nontoxic for retinal pigment epithelium cells, and intraperitoneal and oral use has proven to be neuroprotective in a rat model of retinal degeneration6. One published case report found no clinical signs nor microperimetry changes suggestive of retinal toxicity after two injections in a twelve-week follow-period4.

Electroretinography is noninvasive test useful to evaluate drug toxicity and, from a toxicological standpoint, although classically changes in amplitude and/or latent time by at least 40% must be considered clinically significant7, any reduction in waves amplitudes or increase in implicit time can indicate drug toxicity, and must be carefully investigated. Full-field electroretinography registers the rod or cone system global responses. The International Society for Clinical Electrophysiology of Vision (ISCEV) standardizes protocols that enable an assessment of generalized outer and inner retinal function in dark-adapted and light-adapted conditions8.

Once distinct agents might have different ocular toxicity profiles, safety studies must be carried out for each drug. Herein we report the results of a prospective study that evaluated the safety of intravitreal metoprolol injections in five eyes with circumscribed choroidal hemangioma.

**Methods**

This prospective study adhered to the tenets of the Declaration of Helsinki and was approved by the local research ethics committee. All patients diagnosed with circumscribed choroidal hemangioma presenting with threatening visual macular edema from August 2019 to December 2019 were invited to participate in the study, and written informed consent was obtained before study entry.

Study population
Inclusion criteria were as follows: (1) patients aged > 18 years with circumscribed choroidal hemangioma; (2) refractory to intravitreal anti-VEGF (Becavizumab, Ranibizumab or Aflibercept) injections, (3) no indication to indocyanine green mediated photothermal therapy; (4) refuse external beam radiation and (5) adequate cooperation with the exams performed. Exclusion criteria were as follows: (1) any media opacities that interfere with the proper documentation;(2) any medical condition that preclude the sing of the written informed consent form; (3) history of allergy to metoprolol and/or to others drugs used during the intravitreal injection; (4) pregnancy or planning for pregnancy within one year; and (5) breastfeeding.

Baseline and follow-up evaluations
After eligibility was determined, enrolled patients underwent comprehensive ophthalmologic evaluation at baseline and 4 weeks after the intervention. Baseline and follow-up evaluation included BCVA measurement, applanation tonometry, slit-lamp biomicroscopic examination with anterior chamber cellular score and flare classification, indirect fundus examination with vitreitis classification, color fundus retinography (Cannon CR-2), SD-OCT (Spectralis HRA; Heidelberg Engineering, Heidelberg, Germany), Fundus autofluorescence examination (Spectralis HRA; Heidelberg Engineering, Heidelberg, Germany) and, ISCEV full-field standard protocols (Diagnosys LLC, USA) - dark-adapted: 0.01 cd-s/m2 (ROD), and 3.0 cd-s/m2 (COMBINED), and light adapted (30 cd/m2): 3.0 cd-s/m2 (CONE), and 3.0 cd-s/m2 / 30 Hz (FLICKER) responses.

Intravitreal injections
All injections were performed using topical proparacaine drops under sterile conditions. 5% povidone-iodine drops were applied to the conjunctiva directly five minutes before and immediately after the eye speculum application. The eyelids were scrubbed with 10% povidone-iodine. Metoprolol tartrate (Betacris®, tartarato de metoprolol 1mg/ml, CRISTÁLIA – Produtos Químicos Farmacêuticos Ltda. Itapira, Brazil) 50 mcg/0,05ml was injected into the vitreous cavity using a 29 gauge, 0.5-in needle inserted through the superotemporal pars plana, 3.0 to 4.0 mm posterior to the limbus. Subsequently, central retinal artery perfusion was confirmed with indirect ophthalmoscopy. Patients were instructed to instill one drop of 0.3% ciprofloxacin into the injected eye four times daily for one week after the procedure.

Statistical analysis
BCVA and central subfield values were analyzed using descriptive statistics. All ISCEV recommended ERG parameters a- and b-wave amplitude and implicit time, and oscillatory potentials maximal amplitude for dark-adapted: 0.01 cd-s/m2 (ROD), and 3.0 cd-s/m2 (COMBINED), and light-adapted (30 cd/m2): 3.0 cd-s/m2 (CONE), and 3.0 cd-s/m2 / 30 Hz (FLICKER), were compared using a paired t-test: pre vs. post-treatment.

**Results**

Five eyes with circumscribed choroidal hemangiomas and visual threatening macular edema were enrolled and received intravitreal metoprolol tartrate. Demographic and tumor characteristics, symptoms duration, and previous treatments are summarized in Table 1.

There were no changes in visual acuity and no patient complained of subjective visual acuity reduction, compared to the basal visit. There were no significant changes in color fundus retinography nor fundus autofluorescence with scanning laser ophthalmoscopy. Central subfield foveal thickness decreased in patients one (reduction of 34 μm), two (reduction of 87μm), three (reduction of 10μm), and five (reduction of 27μm) Patient four had an increase of 3μm in the central subfield thickness measurement. Choroidal thickness was stable in all cases. None subject developed anterior chamber cells, flare, or vitreitis. No clinically relevant changes occurred to the intraocular pressure and no systemic side effects were identified.

There was no significant difference between the dark-adapted ROD, COMBINE and OSCILLATORY POTENTIAL responses regarding a and b-wave amplitude and implicit time, measured before and after treatment. There was no significant difference between the light-adapted CONE and FLICKER 30 Hz. responses regarding a and b-wave amplitude and implicit time, measured before and after the treatment as shown in Table 2. Student’s paired t-test p-value were > 0,05 for all comparisons.

 **Discussion**

Intravitreal injections are a new, off label, reported route of administration for beta-blockers agents. It is an attractive route based on a plausible avoidance of systemic side effects, maximizing drug concentration in the vitreous, elimination of the first-pass hepatic metabolism and systemic drug interactions3,4,9.

Regarding retinal toxicity based on electroretinography, Nourinia R. et al. reported a statistically significant decrease of the photopic a- and b-wave amplitudes twenty-eight days after a single intravitreal injection of propranolol (60 μg) in habit eyes. They did not identify electroretinogram changes using lower doses9. Karimi S. et al. treated a patient with retinal capillary hemangioma with propranolol intravitreal injections (50 μg) and reported no prominent electroretinography changes on amplitude and latency of a- and b-waves, comparing baseline with four weeks follow-up tests3. An equivalent dose of metoprolol (50 μg) was used in a patient with circumscribed choroidal hemangioma, without reports of its effect on electroretinography4. To the best of our knowledge, this is the first study to evaluate, *in vivo,* retinal toxicity of metoprolol intravitreal injections.

Patients diagnosed with choroidal hemangioma and visual threatening macular edema, refractory to anti-vascular endothelium growing factor injections and not eligible for laser therapy were enrolled. Once positive outcomes were reported using intravitreal metoprolol injections and the photodynamic therapy is not available in the Brazilian public health system, the authors decided to look into this possible new therapeutic approach.

All subjects, except number 4, had subfoveal involving lesion and symptoms lasting more than six months. According to the published data, long term visual prognosis for circumscribed choroidal hemangioma is guarded10. The approach used in this protocol did not improve the visual acuity of any of the subjects, neither restore the normal subfoveal central macular thickness on SD-OCT. The chronicity of the symptoms might have influenced the results.

The asset of this study is to be the first, *in vivo*, to access retinal toxicity of intraocular metoprolol injections, employing functional and structural tests. Drawbacks are the reduced follow-up period, the use of a metoprolol tartrate dosage based on a single case report published in the literature and the absence of other functional tests (contrast sensitivity tests, color vision tests and microperimetry, e.g.). About those mentioned above, the authors believe that the significant visual impairment caused by the choroidal hemangioma would compromise the results of the tests, making it impossible to bring to light reliable information.

Despite slight changes in structural tests and no visual acuity improvement, metoprolol tartrate at 50 mcg/0,05ml did not show signs of acute ocular toxicity. Different concentrations, drug resistance and tachyphylaxis were not accessed. In conclusion, the off‐label use of intravitreal metoprolol tartrate (50 mcg/0,05ml) may be of interest to possible new therapeutic approaches.

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Table 1. Baseline patients and tumor characteristics. Baseline and final Best Correct Visual Acuity, intraocular pressure, and central subfield foveal thickness.


F = female M = Male BCVA = Best Correct Visual Acuity (Snellen chart) IOP = intraocular pressure CMT = central subfield foveal thickness (ETDRS grid)

Table 2. Comparisons between ISCEV recommended full-field ERG parameters a-wave, b-wave, and dark-adapted oscillatory potentials characteristics pre vs. post metoprolol injection.



ISCEV = International Society for Clinical Electrophysiology of Vision ERG = electroretinography ROD = Dark-adapted 0,01 cd-s/m2 COMBINED = dark-adapted and 3.0 cd-s/m2 OSCILLATORY POTENTIALS = Dark-adapted oscillatory potentials CONE = light adapted (30 cd/m2): 3.0 cd-s/m2 30HZ. FLICKER = light-adapted (30cd/m2) 30 Hz flicker.

*p-value* = Student’s paired t-test p-value.

Figure 1. Baseline and four weeks after the metoprolol injection optical coherence tomography scans of a patient with circumscribed choroidal hemangioma (Patient number 5).



A and C. Baseline optical coherence tomography showing significant thickening of the neurosensory retina causing lost of the normal foveal depression, intraretinal and subretinal fluid accumulation, and disruption of the inner and outer retinal layers a dome shaped choroidal macular tumor. B and D. Optical coherence tomography four weeks after the metoprolol mcg/0,05ml injection showing improvement of the sub-retinal/intraretinal fluid. The vertical scan endorses the fluid reabsorption discarding subretinal fluid gravitational shift.