

Surgical Management of Macular Hole at 2 Years of Follow-Up

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Received date: Sep 14, 2015; Accepted date: Nov 28, 2015; Published date: Dec 01, 2015

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Abstract

Purpose: To determine prognostic factors, anatomic success rate and safety of sutureless pars plana vitrectomy and vitreous base removal associated to internal limiting membrane (ILM) peeling, C3F8 injection and 1-day facedown postoperative positioning to manage idiopathic macular holes (MHs) at 2 years follow-up.

Methods: Forty-six eyes with an idiopathic MH underwent pars plana vitrectomy, ILM peeling after Brilliant Blue 0.05 mg/ml staining, and gas tamponade. Patients remained facedown for 1 day postoperatively. Follow-up included measurement of best-corrected visual acuity (BCVA) and optical coherence tomography (OCT) at 1 and 7 days and 1, 6, 12, and 24 months postoperatively. If the MHs were not anatomically closed by 1 month, another procedure was performed.

Results: Primary and final anatomical closure rate were 91.3% and 97.8%, respectively. Mean BCVA improvement (logarithm of the minimum angle of resolution, LogMAR) was 0.34. No late MH reopening occurred, no surgery-related or ocular dye-related complications developed. The BCVA was less likely to improve in MHs with longer symptomatic periods or larger internal diameters.

Conclusion: Pars plana vitrectomy combined with vitreous base removal and ILM peeling using Brilliant Blue 0.05% associated to C3F8 injection and 1-day facedown postoperative positioning for idiopathic MHs is a safe surgical approach, achieving a MH closure rate of 91.3% after one procedure and 97.8% after a second one. Long symptoms duration and larger inner MH diameter are associated with poor BCVA.

Keywords: Chromovitrectomy; Brilliant Blue; Macular hole; Vital dyes; Vitrectomy

Summary Statement

Sutureless pars plana vitrectomy associated to posterior hyaloid detachment, internal limiting membrane peeling guided by brilliant blue, staining vitreous base removal, C3F8 injection and 1-day facedown postoperative positioning is a safe and effective surgical technique for management of macular holes.

Introduction

Idiopathic macular holes (MHs) are anatomic defects at the neurosensory central retina extending from the internal limiting layer (ILM) to the retinal pigment epithelium [1]. The physiopathology of MHs is related to anomalous vitreomacular adhesion in primary MHs [2]. Secondary MHs are less frequent and usually related to trauma, laser, or intraocular surgeries. MHs are a significant cause of visual impairment especially in older patients, in whom they develop more frequently [1,2]. MHs are suspected when patients complain of visual impairment, central scotoma or metamorphopsia and confirmed by fundus examination and optical coherence tomography (OCT) [1,2].

Although the original Gass classification [1,2] is still used widely in clinical practice, a new classification based on OCT findings was reported recently [3]. This classification considers the presence or

absence of vitreomacular traction (VMT), size, and MH etiology. In this OCT-based anatomic classification system, MHs are defined as small when the minimal width is below 250 μm , medium from 250-400 μm , and large over 400 μm . MHs also are classified as having or not having VMT and as primary or secondary forms.

In MH smaller than 250 μm with VMT associated, observation or injection of Ocriplasmin (Jetrea, ThromboGenics, and Iselin, NJ) may be attempted to release the anomalous adhesion [3]. If there is no VMT, vitrectomy is the only option for restoring normal central retinal architecture [3]. The first surgical procedure to repair MHs by relieving VMT and promoting re-apposition of the MH edges was reported in 1991 [4]. Surgery for MHs typically includes removal of any epiretinal membranes (ERMs) and peeling of the ILM, with or without use of vital dyes to aid visualization [5-10]. Vitreous substitutes are usually used at the end of surgery as intraocular tamponade and they include octafluoropropane (C3F8), sulfur hexafluoride (SF6), silicon oil, or filtered air. Patients are instructed to maintain a facedown position for one to seven days postoperatively to optimize the effect of the gas bubble on the macula and increase the likelihood of successful MH closure [3,4]. Complications of the surgical procedure include development of cataract, retinal tears, retinal detachment, MH persistence or recurrence, and visual field defects [3,4].

The probability of anatomically successful MH closure postoperatively seems to be strictly related to the size, duration, and stage of the MH and patient age. With recent advances in retinal

surgery, small MH have high closure rates approaching 100%, medium MHs over 90%, and large MHs 90% to 95% [3].

A variety of dyes including trypan blue, Brilliant Blue, and lutein-based dyes can be used to aid visualization of the ILM [5-7]. The dyes have varying degrees of ILM specificity and may be used sequentially to peel ERMs, if present, and then ILMs [8,9]. Brilliant Blue is a blue anionic aminotriarylmethane chemical compound with affinity for staining the ILM with small acceptable signs of toxicity [10]. In humans, Brilliant Blue produced appropriate ILM staining in an iso-osmolar solution of 0.25 mg/ml when used for idiopathic ERMs and MHs [5-10].

The objective of the current study was to determine prognostic factors, anatomic success and safety of sutureless pars plana vitrectomy and vitreous base removal associated to internal limiting membrane (ILM) peeling to manage idiopathic macular holes (MHs) at 2 years follow-up.

Methods

We retrospectively evaluated 46 eyes of 46 consecutive patients between January 2012 to January 2013 with a diagnosis of MH and performed PPV with ILM peeling using a soluble formulation of Brilliant Blue 0.05 mg/ml (Ophthalmos, Sao Paulo, Brazil). Table 1 shows the preoperative patient data.

The Ethics Committee of the Federal University of São Paulo approved the study, which was conducted according to the research guidelines of the Association of Research in Vision and Ophthalmology and the tenets of the Declaration of Helsinki. All patients provided informed consent regarding the benefits and risks of the surgical procedure and dye used.

	n	Percentage (%)
Men	8	17
Age (years)	64 (range, 24-82)	
Symptom duration (months)	3 (range, 1-24)	
Preoperative internal diameter (microns)	457 (range, 135-954)	
Preoperative height (microns)	398 (range, 192-587)	
Macular status (Gass classification) ¹		
MHG II	9	19.5
MHG III	22	47.8
MHG IV	15	32.6
Macular status (IVTS classification system) ³		
Small MH	8	17.3
Medium MH	23	50
Large MH	15	32.6
Fellow-eye status		
Normal	32	70
MHG I to IV	14	30
Lens status		
Phakic and no cataract	6	13
Phakic and cataract	13	28
Pseudophakic	27	59
Associated ERM	10	22
Associated macular edema	19	41
MHG: Macular Hole Grade; IVTS: International Vitreomacular Traction Study; ERM: Epiretinal Membrane		

Table 1: Patient demographic characteristics.

Inclusion criteria were: both genders, older than 18 years, not pregnant, and required an elective pars plana vitrectomy to treat a MH with 0.05 or better BCVA (LogMAR), and duration of symptoms for less than 2 years. Exclusion criteria were: any ocular condition that could limit or affect the postoperative results, such as window defects caused by any degree of RPE atrophy affecting the macular area observed by fluorescein angiography, co-morbidities such as optic nerve atrophy, advanced glaucoma, and previous ocular surgery other than cataract extraction.

All patients were submitted to an ocular examination performed preoperatively and 1 and 7 days, 1, 6, 12, and 24 months postoperatively, which included measurement of the BCVA using the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart and Snellen charts as well as slit-lamp and fundus evaluations. All BCVA measurements were converted to logMAR equivalents of the Snellen VA for analysis. Spectral-domain OCT also was performed during each visit using Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany), unless media opacities were present. OCT measurements included MH diameter and MH height.

Surgical procedure

Surgeries were carried out by two experienced vitreoretinal surgeons (OMB and MM) using binocular indirect ophthalmomicroscope (BIOM System, Oculus, Wetzlar, Germany). Because nuclear cataracts commonly develop after vitrectomy, phacovitrectomy was performed in all 19 phakic eyes using a 2.4-mm clear corneal incision with implantation of an aspheric intraocular lens (Akreos AO, Bausch & Lomb, Rochester, NY). The incision was not sutured at the end of phacoemulsification. A 4-port PPV using 23-gauge valved trocars and one accessory 23-gauge chandelier light pipe was performed.

In cases in which the posterior hyaloid was attached to the posterior pole, 0.1 ml of triamcinolone acetonide was injected into the vitreous cavity to stain the posterior hyaloid. Shaving the vitreous base was performed with the help of scleral indentation (Figure 1).

Conversely to a standard concentration of 0.025%, 0.3 ml of Brilliant Blue 0.05% (Ophthalmos, Brazil) were flushed through the posterior pole using a soft tip cannula (Synergetics, USA) while the infusion cannula was disconnected from the infusion system, with care to avoid injection directly into the hole (Figure 1).

For macular surgery, a Machemer contact lens (Volk, Cleveland, OH) was used and ILMs were peeled using an intraocular 23-gauge forceps. The ILM peeling was initiated by grasping the ILM over the inferior macular region with the forceps; the peeling then was extended in a circumferential manner over the area, including the macula; in any case, residual ILM around the macular was observed intraoperatively Figure 1.

Once the ILM was completed and after a fluid/air exchange, C3F8 15% was injected into the vitreous cavity. Finally, both trocars and chandelier pipe were removed and no sutures were placed. The patient was instructed to maintain one day face-down position.

In cases in which MH closure was not achieved within 30 days postoperatively, a second vitrectomy was performed. The technique used for this procedure was the same as that for the first, except that the area of ILM peeling was enlarged after staining with Brilliant Blue. C3F8 15% was used and patients were instructed to maintain facedown position for 5 days.

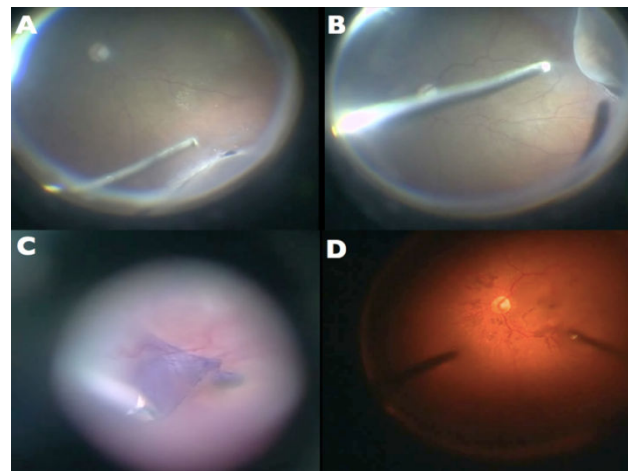


Figure 1: a/b. Shaving of the vitreous base aided by an indentation maneuver performed by the surgeon, c. Internal limiting membrane peeling during phacovitrectomy with 0.3 ml of 0.05% Brilliant Blue staining under the visualization of the Stellaris PC (Bausch & Lomb) ambar filter, d. Visualization of the retina after internal limiting membrane.

Statistical analysis

Multiple logistic regression analysis was performed to determine the chances of an increase in BCVA as a function of demographics and preoperative variables. $P < 0.05$ was considered statistically significant. The association between the duration of symptoms and the minimum diameter of the MH with the percentage of patients with improved BCVA was analyzed using the chi-square test. Analyzes were made using SPSS v15.0 software (SPSS Inc., Chicago, IL).

Results

The mean age of the 46 patients (38 women, 8 men) was 64 years (range, 24-82 years). Considering The International Vitreomacular Traction Study Group Classification of Vitreomacular Adhesion, Traction, and Macular Hole, [2] eight eyes had small MHs, 23 had medium MHs, and 15 had large MHs (Table 1). The mean preoperative BCVA (LogMAR) was 0.16 (range, 0.02-0.40); the mean final BCVA (LogMAR) 24 months postoperatively was 0.5000 (range, 0.05-1.00). BCVA increased in all patients with a mean BCVA (LogMAR) improvement of 0.34 and all eyes were followed for at least 24 months (range, 24-81 months) (Table 2). In a subgroup analysis comparing the BCVA improvements in phakic and no cataract ($n=6$) and pseudophakic ($n=27$) patients, the first group achieved better results, although this finding was not significant and expected, as all phakic patients underwent combined phacovitrectomy which avoided the development of cataract that could decrease the BCVA afterwards (Table 3).

Patients with symptom durations ranging from 1 to 2 months preoperatively had more significant improvements in final BCVA compared to those with longer symptomatic periods (odds ratio, 0.21 range, 0.05-0.77; $P=0.019$); preoperative MH height did not significantly affect visual function outcomes after surgery.

	No. eyes	Percentage (%)
23-gauge surgery	46	100
ILM peeling with Brilliant Blue 0.05%	46	100
Gas tamponade octafluoropropane	46	100
Combined cataract surgery	19	41
Preoperative logMAR BCVA	0.16 (0.02-0.40)	
24-month follow-up logMAR BCVA	0.50 (0.05-1.00)	
Mean increase in Snellen BCVA	0.34 (0.00-0.90)	
ILM: Internal Limiting Membrane; logMAR BCVA: Logarithm of the Minimum Angle Of Resolution Visual Acuity		

Table 2: Intraoperative and postoperative patient characteristics.

	Phakic and cataract (n=6)	Pseudophakic (n=27)	P value
Preoperative BCVA	0.15	0.2	0.52
24month BCVA	0.56	0.5	0.47
Difference in BCVA after 24 months	0.41	0.25	0.11
BCVA: Visual Acuity. P values<0.05 were considered statistically significant.			

Table 3: Comparison between mean visual acuity in phakic and pseudophakic patients at baseline and after 24-month follow-up period. Note that 13 phakic eyes with cataract were excluded from the BCVA comparisons.

Twenty-four months postoperatively, no abnormalities suggestive of dye toxicity were observed during clinical evaluations. Since MH did not close by 30 days after the first procedure in 4 patients, a second surgical approach was performed in these cases. The ILM peeling was extended around the edges of the previous peeling for around more 1-2 discs area and C3F8 15% was injected at the vitreous cavity following by additionally 3 days of prone positioning postoperatively. MH closure was achieved in three of them. No MH reopened, and no retinal detachment or other complications developed in association with vitrectomy.

Discussion

As one of the purposes of this study was to show that vitreous base removal may be important in macular hole surgery due to the possibility to decrease the risks of future tears at the periphery as well as retinal detachments, we also included pseudophakic eyes because we were able to get access to the vitreous base in such eyes; similarly, in all phakic eyes we've performed associate phacoemulsification in order to be able to get access to the vitreous base; in fact, in both groups either pseudophakic or phakic submitted to combined surgery, we were able to get access to vitreous base and the outcome in both groups were similar ($p>0.05$); additionally, we did not observe cases of retinal detachment after surgery at 2 years follow up.

Brilliant Blue is fast emerging as the most popular dye used worldwide among the current available dyes to stain ILMs during vitrectomy performed to treat several macular pathologies [14]. However, it is well known that any dye can cause retinal toxicity and therefore should be used in minimal amounts and concentrations for the shortest possible time and with the most favorable pH and osmolality [15] Nevertheless, no signs of toxicity (including RPE abnormalities at the subfoveal area) were observed during the follow-up period by clinical examination or OCT in this study.

Recent modifications of the dye characteristics have been attempted to achieve better staining of the ILM. The current options are to increase the dye sedimentation at the posterior pole by adding heavy water (deuterium oxide), [16,17] using 10% dextrose, [18] performing air-fluid exchange, [9] and increasing the dye concentration [8].

The main disadvantage of air-fluid exchange is the increased risk for surgical complications including retinal tears [19]. To eliminate the need for air-fluid exchange, we proposed increasing the dye concentration that can be applied to the retinal surface with good capability to stain the ILM in an eye filled with fluid.

In the current study, we performed vitrectomy with peeling of the ILM using Brilliant Blue in a higher concentration than usual, i.e., 0.05 mg/ml, instead of the conventional 0.025 mg/ml. The success rates were comparable to previous success rates with no signs of ocular or systemic toxicity. The anatomic closure rates after the first surgery were 91.3% in 42 of 46 eyes, and 97.8% after the second surgery in 45 of 46 eyes, which is consistent with previous reports in the literature. If a second procedure was necessary, it was performed with enlargement of the area of the ILM to be peeled using the same Brilliant Blue 0.05% dye, gas tamponade, and a longer facedown positioning (3 days instead of only 1 day as suggested after the first surgery) postoperatively.

The mean preoperative BCVA was 0.16 logMAR, which improved to 0.50 logMAR after 24 months of follow-up (Table 2). No patient had decreased BCVA. The visual outcomes were significantly ($P<0.05$) better in patients with small MHs compared with those with large MHs. No MHs reopened in the current series, and no retinal detachment or other complications developed as a result of the vitrectomy.

All subjects underwent phacovitrectomy, except those who were pseudophakic. We believe that this is a feasible surgical technique that avoids a second cataract surgery, which is necessary in around 90 percent of eyes from patients more than 60 years old at 2 years follow-up [20]. Additionally, the vitreous base access allows the identification of possible iatrogenic retinal tears that may be sealed to minimize the possibility of retinal detachment [20]. The preliminary observation of no retinal tears or detachment at 2-years follow up is an important finding and we hypothesized that this may be related to the vitreous base shaving. However, additional studies are necessary to validate this hypothesis [21]. Although intraoperative use of triamcinolone and its presence during the follow-up period may be related to delayed closure and reopening of MHs [22,23] those did not occur in our group of patients.

Chromovitrectomy is undergoing constant improvements, and studies are performed constantly. Recently, our group reported use of lutein-based dyes as an alternative for ILM dyeing, with good staining ability and good safety profiles [5-7,24]. Future research on the healing process in MH surgery to compare dyes for ILM peeling and innovative adjuvants to improve the healing process and investigate

substances that may be helpful to stimulate photoreceptors growth will facilitate understanding and optimize better treatment for MHs.

By our knowledge, this is the first study that performed a combination sutureless pars plana vitrectomy, posterior hyaloid detachment, bimanual vitreous base removal guided by triamcinolone acetonide as well as ILM peeling guided by 0.05mg/mL of BB staining and also C3F8 intravitreal injection followed by 1 day facedown postoperative prone position.

The strengths of our study were that we evaluated a novel concentration of Brilliant Blue 0.05 mg/ml with a good safety profile in a relative large number of patients, associated to vitreous base removal in all cases and a long follow-up period. The limitations were that two surgeons performed the surgeries and there was no control group available.

Despite different surgeons may be a BIAS factor, we had decided to include the data performed by 2 surgeons in order to demonstrate that surgical technique is reproducible. The lack of control group using 0.025% of brilliant blue is explained by the retrospective design and that majority of reports in the literature already used this lower concentration of 0.025% successfully. Similarly, the lack of control group with no ILM peeling is explained both by the retrospective design and that gliosis induction at the macular hole - resulting in closure - is related to a combination of 3 factors reported in the literature: 1-Vitreous removal when it is attached (stages 1-3); 2-removal of ILM in stages 3 and 4; and 3- postoperative positioning (which is unclear in the literature if is necessary for all cases). As we've decided that factor 3 of gliosis induction should be standardized by 1 day of postoperative positioning only and this could result in a decrease at the in success rates of macular hole sealing, we've decided to peel the ILM in all cases to achieve higher closure rates; however, we are aware that literature had already provided scientific evidence that eyes with stage II macular hole and postoperative positioning for more than one day may not be submitted to ILM peeling.

In conclusion, pars plana vitrectomy combined with vitreous base removal, ILM peeling using Brilliant Blue 0.05% and C3F8 injection associated with 1 day facedown postoperative positioning for idiopathic MHs was safe and reached anatomical success of 91.3% after one surgical procedure and 97.8% after two procedures as well as no retinal detachment at 2 years follow up. A long symptom duration and larger inner MH diameter were associated with worse BCVA levels. Additional larger prospective studies are necessary to confirm these preliminary findings.

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References

- Gass JD (1995) Reappraisal of biomicroscopic classification of stages of development of a macular hole. *Am J Ophthalmol* 119: 752-759.
- Gass JD (1988) Idiopathic senile macular hole. Its early stages and pathogenesis. *Arch Ophthalmol* 106: 629-639.
- Duker JS, Kaiser PK, Binder S, de Smet MD, Gaudric A, et al. (2013) The International Vitreomacular Traction Study Group Classification of Vitreomacular Adhesion, Traction, and Macular Hole. *Ophthalmology* 120: 2611-2619.
- Kelly NE, Wendel RT (1991) Vitreous surgery for idiopathic macular holes. Results of a pilot study. *Arch Ophthalmol* 109: 654-659.
- Badaro E, Furlani B, Prazeres J, Maia M, Lima AA, et al. (2014) Soluble lutein in combination with brilliant blue as a new dye for chromovitrectomy. *Graefes Arch Clin Exp Ophthalmol* 252: 1071-1078.
- Maia M, Furlani BA, Souza-Lima AA, Martins DS, Navarro RM, et al. (2014) Lutein: a new dye for chromovitrectomy. *Retina* 34: 262-272.
- Sousa-Martins D, Maia M, Moraes M, Lima-Filho AA, Rodrigues EB, et al. (2012) Use of lutein and zeaxanthin alone or combined with Brilliant Blue to identify intraocular structures intraoperatively. *Retina* 32: 1328-1336.
- Rodrigues EB, Costa EF, Penha FM, Melo GB, Bottós J, et al. (2009) The use of vital dyes in ocular surgery. *Surv Ophthalmol* 54: 576-617.
- Farah ME, Maia M, Rodrigues EB (2009) Dyes in ocular surgery: principles for use in chromovitrectomy. *Am J Ophthalmol* 148: 332-340.
- Badaro E, Novais EA, Penha FM, Maia M, Farah ME, et al. (2014) Vital dyes in ophthalmology: a chemical perspective. *Curr Eye Res* 39: 649-658.
- Heimann H, Bartz-Schmidt KU, Bornfeld N, Weiss C, Hilgers RD, et al. (2007) Scleral buckling versus primary vitrectomy in rhegmatogenous retinal detachment: a prospective randomized multicenter clinical study. *Ophthalmology* 114: 2142-2154.
- Campo RV, Sipperley JO, Sneed SR, Park DW, Dugel PU, et al. (1999) Pars plana vitrectomy without scleral buckle for pseudophakic retinal detachments. *Ophthalmology* 106: 1811-1815.
- Bernheim D, Rouberol F, Palombi K, Albrieux M, Romanet JP, et al. (2013) Comparative prospective study of rhegmatogenous retinal detachments in phakic or pseudophakic patients with high myopia. *Retina* 33: 2039-2048.
- Rodrigues EB, Penha FM, de Paula Fiod Costa E, et al. (2010) Ability of new vital dyes to stain intraocular membranes and tissues in ocular surgery. *Am J Ophthalmol* 149: 265-277.
- Penha FM, Maia M, Eid Farah M, Príncipe AH, Freymüller EH, et al. (2007) Effects of subretinal injections of indocyanine green, trypan blue, and glucose in rabbit eyes. *Ophthalmology* 114: 899-908.
- Peláyes DE, Kuhn F, Folgar AM, Takahashi W, Bastien A, et al. (2012) Staining of the internal limiting membrane with the use of heavy brilliant blue G. *Ophthalmic Res* 48: 21-25.
- Haritoglou C, Schumann RG, Kampik A, Gandorfer A (2011) Heavy brilliant blue G for internal limiting membrane staining. *Retina* 31: 405-407.
- Costa Ede P, Rodrigues EB, Farah ME, Dib E, Penha F, et al. (2009) Vital dyes and light sources for chromovitrectomy: comparative assessment of osmolarity, pH, and spectrophotometry. *Invest Ophthalmol Vis Sci* 50: 385-391.
- Lesnik Oberstein SY, Mura M, Tan SH, de Smet MD (2007) Heavy trypan blue staining of epiretinal membranes: an alternative to infracyanine green. *Br J Ophthalmol* 91: 955-957.
- Bhatnagar P, Kaiser PK, Smith SD, Meisler DM, Lewis H, et al. (2007) Reopening of previously closed macular holes after cataract extraction. *Am J Ophthalmol* 144: 252-259.
- Guillaubey A, Malvitte L, Lafontaine PO, Hubert I, Bron A, et al. (2007) Incidence of retinal detachment after macular surgery: a retrospective study of 634 cases. *Br J Ophthalmol* 91: 1327-1330.
- Yamauchi Y, Nakamura H, Hayakawa K, Sawaguchi S (2006) Persistence of triamcinolone acetonide following macular hole surgery. *Acta Ophthalmol Scand* 84: 711-712.
- Koto T, Inoue M, Shinoda K, Ishida S, Tsubota K (2007) Residual crystals of triamcinolone acetonide in macular hole may prevent complete closure. *Acta Ophthalmol Scand* 85: 913-914.
- Caseli L, Sousa-Martins D, Maia M, Lima-Filho AA, Rodrigues EB (2013) An intraocular dye solution based on lutein and zeaxanthin in a surrogate internal limiting membrane model: a Langmuir monolayer study. *Colloids and surfaces B Biointerfaces* 107: 124-129.

