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RETINAL DISORDERS

Combined pars plana vitrectomy (PPV) and phacoemulsification (phaco) versus PPV and deferred phaco for phakic patients with full-thickness macular hole (FTMH) and no significant cataract at baseline: 1-year outcomes of a randomized trial combined PPV/phaco vs PPV/deferred phaco for MH

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Abstract

Purpose To compare functional and anatomic outcomes of combined pars plana vitrectomy (PPV) and phacoemulsification (phaco) versus PPV and deferred phaco in patients with full-thickness macular hole (FTMH) and no significant cataract.

Methods Thirty-four patients were randomized to group 1 (combined PPV/phaco) and 34 to group 2 (PPV/deferred phaco). Group 2 patients could undergo phaco any time after FTMH surgery if significant cataract developed.

Results Sixty-five patients (33 group 1 and 32 group 2) completed the 12-month visit. Mean ± SEM logMAR best-corrected visual acuity (BCVA) was 0.92 ± 0.04 and 0.90 ± 0.04 at baseline and improved significantly to 0.60 ± 0.05 and 0.58 ± 0.05 at month 12 ($p < 0.0001$) in groups 1 and 2, respectively. There was no significant difference between the groups in mean BCVA at baseline or at month 12. Mean macular sensitivity (dB) was 18.22 ± 0.93 and 16.72 ± 0.93 at baseline and increased to 21.13 ± 0.86 and 21.07 ± 0.85 in groups 1 and 2, respectively ($p < 0.05$) with no significant difference between the groups ($p = 0.449$) at month 12. FTMH closure rate was 73% and 75% in groups 1 and 2, respectively ($p = 0.834$).

Conclusion Among patients with FTMH and no significant cataract at baseline, combined PPV/phaco was associated with similar BCVA, microperimetry, and FTMH closure outcomes at 1-year compared with PPV/deferred phaco.

Trial registration (clinicaltrials.gov.br): Ensaios clínicos brasileiros: RBR-3wmd9s; UTN number: U1111-1190-5013; Plataforma Brasil CAAE number: 50455415.3.0000.5440; IRB number: 1.433.000.

Keywords Vitrectomy · Phacoemulsification · Macular hole · Combined surgery

Introduction

Full-thickness macular hole (FTMH) was observed in approximately 0.3% of people older than 42 years in a study cohort in Beaver Dam, Wisconsin [1], and had an incidence of 0.7% per decade in persons aged 40 years or older in a study cohort in Baltimore, Maryland [2]. While its etiology is not completely understood, tangential and anteroposterior vitreomacular traction have been reported to be important contributing factors [3–5]. The most common symptoms of FTMH are central scotoma and metamorphopsia.

Pars plana vitrectomy (PPV) is an effective treatment for FTMH in most cases. However, significant cataract develops in over 50% of patients within 2 years postoperatively, such that a second surgical procedure (cataract surgery) is often needed for visual rehabilitation [6–8].

Previous authors have reported that combined PPV and phacoemulsification (phaco) is associated with low morbidity and favorable visual and anatomic outcomes in phakic

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patients with FTMH [9, 10]. The purpose of the present study is to evaluate outcomes of combined PPV/phaco versus PPV/deferred phaco in phakic patients with FTMH and no significant cataract at baseline.

Methods

The study adhered to the tenets of the Declaration of Helsinki, Institutional Review Board approval of the protocol was obtained, and written informed consent was obtained from all participants. All phakic patients with FTMH and no cataract or with lens opacity < grade II cortical/nuclear of the Lens Opacity Classification System (LOCS) III [11] and who were scheduled to undergo surgery for FTMH at the University of Sao Paulo School of Medicine of Ribeirão Preto between March 3, 2016, and March 1, 2017 were invited to participate in the study. Patients were randomized to either combined PPV/phaco (group 1) or PPV/deferred phaco (group 2). All patients received a number and each number was allocated by a computer-generated sequence. Patients and surgeons were not masked, but the researcher who measured the BCVA after surgery was masked.

Inclusion/exclusion criteria and baseline evaluation

Inclusion criteria

Inclusion criteria included the following: (1) symptomatic patients with idiopathic FTMH stage II or higher [12]; (2) BCVA worse than 0.2 logMAR; and (3) no cataract or lens opacity LOCS III [11] cortical ≤ 2, nuclear ≤ 2, and no subcapsular opacity.

Exclusion criteria

Exclusion criteria include the following: (1) any ophthalmic disease other than FTMH or lens opacity specified in the inclusion criteria; (2) previous ocular surgery; (3) any condition that, in the investigator's opinion, may preclude follow-up for 12 months after FTMH surgery.

All patients underwent comprehensive ocular examination including assessment of Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA, Goldmann applanation tonometry, slit-lamp examination, and dilated indirect funduscopic examination. Full-thickness macular hole measurements including height, minimum linear diameter or internal base (IB) and external base diameter (EB: the largest linear distance between macular hole external retina margins) were obtained using spectral-domain optical coherence tomography (SD-OCT) (Heidelberg, Heidelberg, Germany). Macular sensitivity was measured using a MAIA microperimeter (MAIA Centervue, Italy).

Macular sensitivity was assessed within the 6° central macular field using the 37-point grid expert examination protocol of the MAIA microperimeter (MAIA Centervue, Italy).

Patients in group 1 underwent combined PPV and phaco followed by implantation of a three-piece intraocular lens (IOL) while patients in group 2 underwent PPV and could receive phaco followed by implantation of a three-piece IOL at any time postoperatively if cataract severity was LOCS III subcapsular ≥ 1 or nuclear ≥ 3 or cortical ≥ 3, or if, in the investigator's opinion, the patient had (1) cataract that would prevent accurate ophthalmologic examination, OCT, or microperimetry; or (2) clinically significant decrease in visual acuity attributable to cataract. Patients in both groups were followed for 1 year following PPV.

Surgical technique

All surgeries were performed by one of two vitreoretinal surgeons. Anesthesia consisted of a peribulbar block with 10 mL 2% bupivacaine in combination with intravenous sedation administered by an anesthesiologist. PPV was performed with three sclerotomies and 23-gauge instruments, with no suture. The posterior hyaloid was stained with triamcinolone acetonide and detachment was attempted in all patients without a pre-existing posterior vitreous detachment. Brilliant blue dye was used to stain the internal limiting membrane, which was then peeled for 360° around the FTMH in an oval shape with the largest diameter around 4 to 5 mm, and 15% C3F8 gas was injected into the vitreous cavity at the end of the vitrectomy. The amount of gas injected into the vitreous cavity was regulated from a 20-ml calibrated syringe. Fluid-air exchange was performed in patients in both groups with this system. Patients were instructed to maintain face-down positioning for at least 7 days postoperatively.

Cataract surgery was performed by the same aforementioned surgeons via a clear cornea incision constructed with a 2.75-mm blade, anterior capsulorhexis, and then phacoemulsification (Infiniti/Constellation machines, Alcon) using the "stop and chop" technique followed by implantation of a three-piece IOL (MA60AC Type 7B, Alcon, Fort Worth, Texas) in the capsular bag. The IOL power was calculated to induce a final refraction of minus 0.5 spherical diopters. A 10.0 nylon suture of the clear cornea incision was placed in patients from group 1 before PPV and was removed at the end of surgery.

Follow-up examinations and outcome measures

Patients were scheduled for follow-up examinations at baseline (T_0) before surgery and at 1 month (T_1), 3 months (T_3), 6 months (T_6), 9 months (T_9), and 12 months (T_{12}) post-PPV. Follow-up examinations included comprehensive ocular examination using the same assessments as at baseline. The main outcome measure was change from baseline in logMAR BCVA. Secondary outcome measures included average threshold change (dB) and macular hole closure rate (%).

Sample size estimation

The sample size of 34 patients per group was based on the standard deviation of visual acuity gain from a study of long-term results of FTMH surgery by Chawla et al.: 0.14 logMAR [13]. With this sample size, the study had 80% power to detect a minimum difference of 0.14 logMAR (6 letters) between groups, with a significance level set at $p < 0.05$.

Statistical analysis

BCVA, macular sensitivity threshold, and intraocular pressure (IOP) at each follow-up visit were compared with baseline values and between groups. Comparisons were performed using two-way analysis of variance for repeated measurements (ANOVA-RM). Statistical significance was set at a value of $p < 0.05$. Statistical analyses were performed using JMP ® 10 (SAS Institute Inc. Cary, NC, USA).

Patient involvement

The research question and outcome measures were explained clearly to all patients, each of whom had the opportunity to ask any questions before inclusion. Improvement of BCVA and macular hole closure were the main benefits discussed, as well as possible side effects such as retinal detachment, posterior capsule rupture and failure of macular hole closure. Patients were not involved in the recruitment or conduct of the study but were informed about the results and progress of their disease during the study.

Results

Seventy-four phakic patients with FTMH were identified during the study period. Baseline characteristics are summarized in Table 1. Six patients declined study participation. Sixty-eight patients were randomized to either group 1 (combined PPV/phaco; $n = 34$) or group 2 (PPV/deferred phaco; $n = 34$). Three patients were excluded from study analysis (2 patients were lost to follow-up and 1 patient was unable to perform the tests correctly). Data from 33 patients from group 1 and 32 patients from group 2 were included in the final analysis (Fig. 1). At baseline, patients' reported duration of decreased vision was 11.78 months and 12.25 months in groups 1 and 2, respectively ($p = 0.875$). One, five, five, and 16 patients from group 2 had cataract surgery, as per protocol criteria, at the first, second, third and fourth trimesters of study follow-up, respectively. Five patients from group 2 did not meet criteria for cataract surgery during the 1-year of study follow-up.

Outcome measures

Best-corrected visual acuity

At baseline, mean ± standard error logMAR BCVA was 0.92 ± 0.04 and 0.90 ± 0.04 in groups 1 and 2, respectively, with no significant difference between groups. Improvement in intragroup mean BCVA compared with baseline was observed after surgery at all follow-up visits in groups 1 and 2 ($p < 0.05$). At month 6, mean BCVA improvement was significantly higher in group 1 patients compared with group 2 (group 1 0.64 ± 0.05; group 2 0.79 ± 0.05) ($p = 0.027$). At month 12, mean BCVA was significantly improved compared with baseline in both groups (group 1 0.60 ± 0.05; group 2 0.58 ± 0.05), with no significant difference between the groups ($p = 0.842$) (Fig. 2).

Spherical equivalent

At baseline, mean ± standard error spherical equivalent was 0.90 ± 0.3 and 0.81 ± 0.3 in groups 1 and 2, respectively, with no significant difference between the groups ($p = 0.975$). A decrease in intragroup mean spherical equivalent compared with baseline was observed after surgery at all follow-up visits in groups 1 and 2 ($p < 0.001$). There was no significant difference in spherical equivalent between the groups at any of the study visits. At month 12, spherical equivalent was significantly decreased compared with baseline in both groups (group 1 − 0.68 ± 0.19; group 2 − 1.11 ± 0.19), with no significant difference between the groups ($p = 0.229$) (Fig. 3).

Spherical equivalent versus predicted refraction

At month 1 (all patients from group 1 and no patients in group 2 had undergone cataract surgery), the mean difference between the spherical equivalent and the predicted refraction (− 0.5 spherical diopters) was − 0.28 ± 0.16 and 0.13 ± 0.36 ($p = 0.313$), in groups 1 and 2, respectively. At month 3 (1 patient in group 2 had undergone cataract surgery), the same difference was − 0.22 ± 0.17 and 0.03 ± 0.42 ($p = 0.583$), at month 6 (total of 6 patients in group 2 had undergone cataract surgery) it was − 0.19 ± 0.17 and – 0.19 ± 0.34 ($p = 1.00$). At month 9 (total of 11 patients in group 2 had undergone cataract surgery), it was −0.22 ± 0.16 and − 0.53 ± 0.35 ($p = 0.424$) and at month 12 (total of 27 patients in group 2 had undergone cataract surgery): − 0.18 ± 0.15 and − 0.61 ± 0.21 ($p = 0.108$).

Astigmatism refractive changes

At baseline, mean ± standard error astigmatism was 0.73 ± 0.11 and 0.93 ± 0.15 in groups 1 and 2, respectively, with no significant difference between groups ($p = 0.29$). No significant change in mean astigmatism compared with baseline was

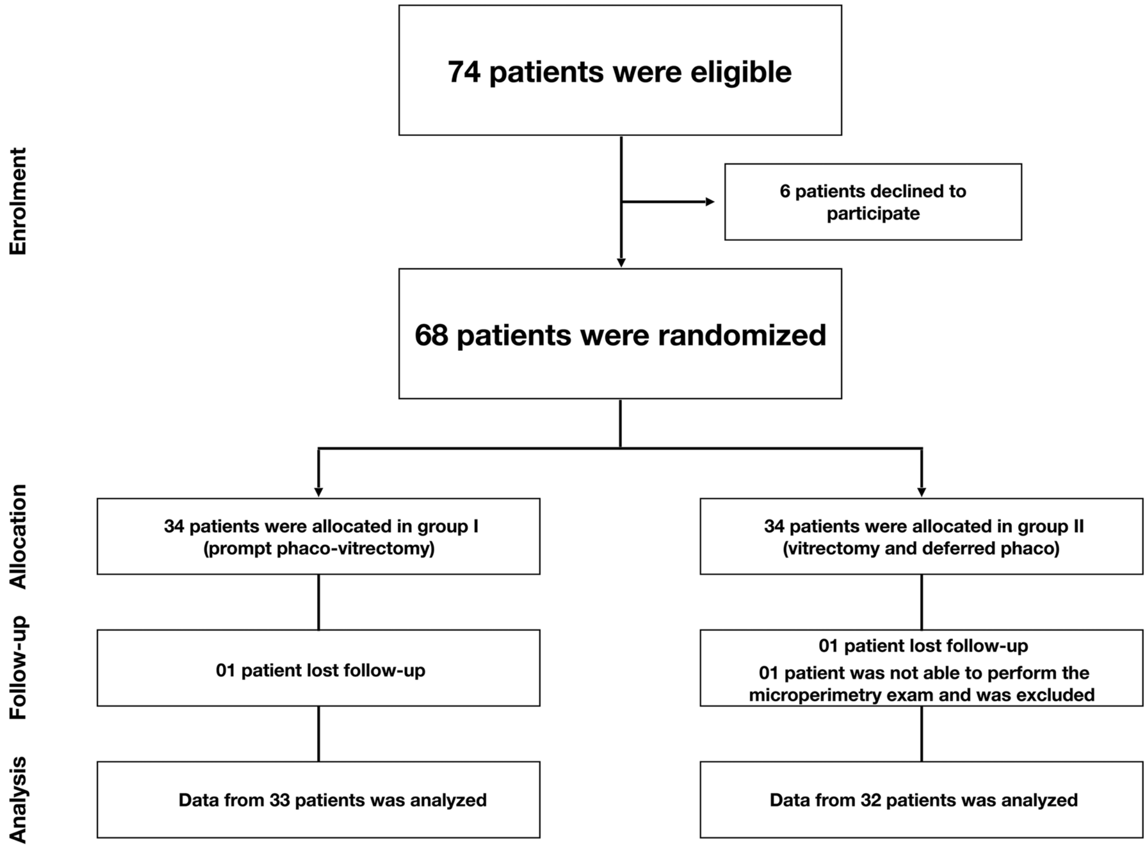

Fig. 1 Flow diagram of patients in both groups through the phases of this parallel randomized clinical trial

observed after surgery at all follow-up visits in groups 1 and 2 ($p > 0.05$). At month 1, mean astigmatism was significantly higher in group 2 patients compared with group 1 ($p = 0.01$). At month 12, mean astigmatism did not differ significantly from baseline in both groups (group 1 0.84 ± 0.13; group 2 0.95 ± 0.13), with no significant difference between the groups ($p = 0.42$).

Macular sensitivity (average threshold—AT)

Preoperative microperimetry in all patients showed an absolute central scotoma corresponding to the FTMH and a surrounding area of relative scotoma. In all patients, fixation was located at the periphery of the FTMH, most often at its upper edge. Baseline mean ± standard error retinal sensitivity (dB)

Table 1 Group characteristics

	PPV/phaco (33)	PPV/deferred phaco (32)	*P*
Gender (female)	26	25	0.94
Mean age ± (std error), years	66.8 ± 1.0	64.6 ± 1.0	0.13
Systemic arterial hypertension (number of patients)	20	19	0.91
Diabetes (number of patients)	7	4	0.34
Symptoms duration (months)	11.8	12.2	0.87
Macular hole classification*			0.96
II	11	9	
III	12	13	
IV	10	10	
Rate of macular hole closure after one PPV procedure	73	75	0.83

* Classfication according to the following manuscript: JDM Gass. Idiopathic senile macular hole: its early stages and pathogenesis. Arch Ophthalmol, 106 (1988), pp. 629–639

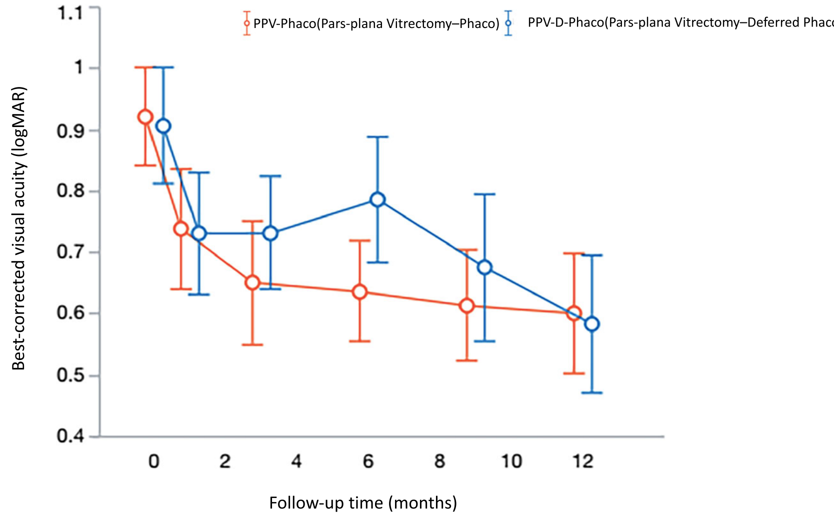

Fig. 2 Mean logMAR BCVA at baseline and throughout the 12-month follow-up period in both study groups. There was mean BCVA improvement in all follow-up visits compared with baseline values in both groups. Six months after surgery, mean BCVA was significantly higher in group 1 (PPV/phaco) than in group 2 (PPV/deferred phaco) patients. For all other study periods, there was no significant difference in mean BCVA between groups

of the macular grid area (6°) was 18.22 ± 0.93 and 16.72 ± 0.93 and improved to 21.13 ± 0.86 and 21.07 ± 0.85 in group 1 and group 2, respectively, at month 12. In both groups, retinal sensitivity improved progressively during follow-up; the improvement from baseline was first significant at 3 months post-PPV and remained significant at each study visit thereafter $p < 0.05$). No statistically significant differences were observed between the groups at any follow-up time point ($p = 0.449$) (Fig. 4).

Macular hole closure rates

At baseline, the mean ± standard error IB of the FTMH was 469.15 ± 34.60 μm and 473.12 ± 35.13 μm in groups 1 and 2, respectively ($p = 0.936$); the mean FTMH EB was 1046.00 ± 61.27 μm and 980.94 ± 62.22 μm, ($p = 0.459$), and the mean FTMH height was 428.51 ± 11.78 μm and 444.75 ± 11.96 μm in groups 1 and 2, respectively ($p = 0.337$), with no significant difference between the groups in any of these measurements.

The FTMH was stage 2 in 33.33% and 28.12% in groups 1 and 2, respectively; stage 3 in 36.36% and 40.62%; and stage 4 in 30.30% and 31.25%, respectively. The FTMH closure rate after a single PPV procedure was 73% and 75% in groups 1 and 2, respectively, at 12 months, with no significant difference between the groups ($p = 0.834$, chi-square test).

Adverse events

In group 1, one patient presented with posterior capsule opacification 6 months postoperatively, two patients with corectopia due to posterior iris synechiae, one patient with a tilted IOL (one IOL border in the sulcus, another inside the capsular bag; both haptics in the bag), and one patient had a significant elevation in IOP (36 mmHg) on the first postoperative day which was controlled with transient use of IOP-lowering medication. In group 2, three patients developed ocular hypertension (IOP of 24, 30, and 34 mmHg) which was controlled with transient use of IOP-lowering medication,

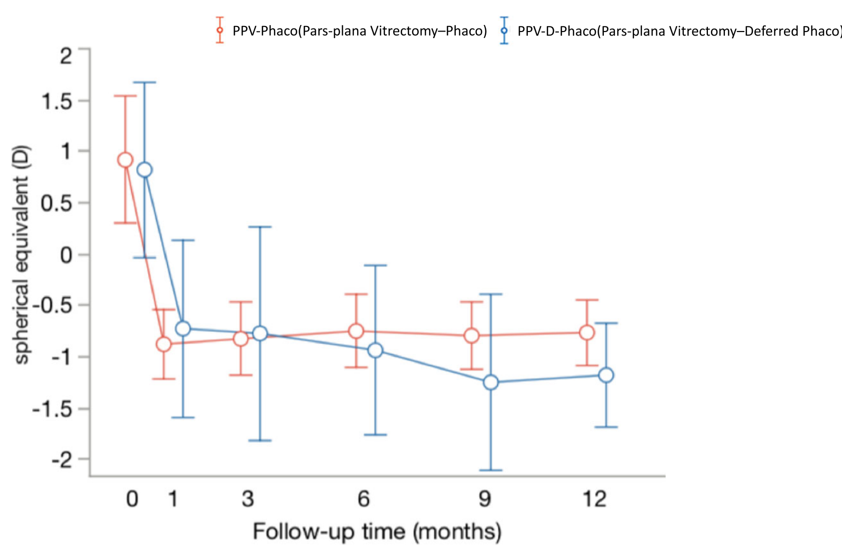

Fig. 3 Mean spherical equivalent at baseline and throughout the 12-month follow-up period in both study groups. A decrease in intragroup mean spherical equivalent compared with baseline was observed after surgery at all follow-up visits in groups 1 and 2. At month 12, spherical equivalent was significantly decreased compared with baseline in both groups (group 1 − 0.68 ± 0.19; group 2 − 1.11 ± 0.19), with no significant difference between the groups ($p = 0.229$)

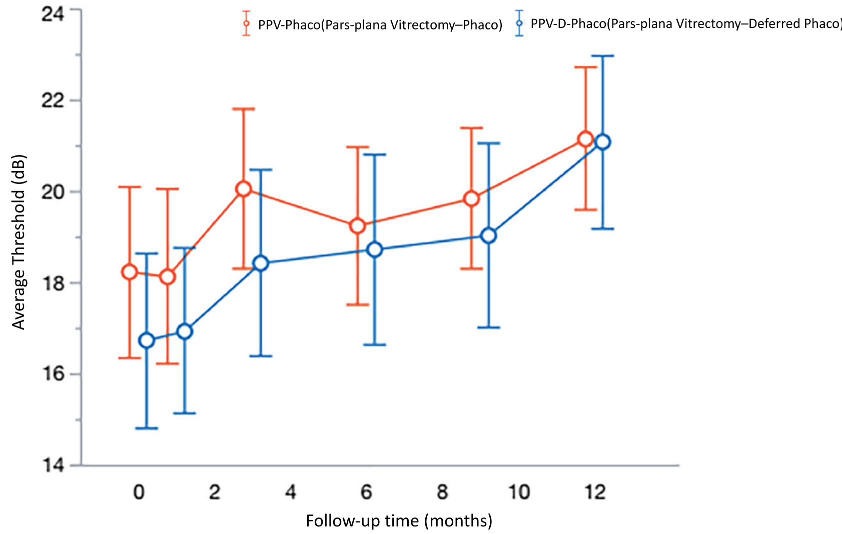

Fig. 4 Change in mean retinal sensitivity threshold (dB) of the 6° macular center during the 12-month-postoperative follow-up period in both study groups. There was mean retinal sensitivity improvement at all follow-up visits compared with baseline values in both groups. For all study periods, there was no significant difference in mean retinal sensitivity between groups

two patients had intraoperative capsular rupture and the IOL was positioned in the sulcus, and one patient presented with anterior uveitis at 1 month after phaco surgery which was controlled with transient use of topical prednisone eye drops.

Discussion

To the best of our knowledge and based on a computerized search of the PubMed literature database, this is the first prospective study comparing the visual acuity outcomes following combined PPV/phaco versus PPV/deferred phaco for phakic patients with FTMH and no significant cataract. Other authors have reported, based on retrospective chart reviews studies, that combined PPV and phaco is associated with similar BCVA outcomes when compared with PPV and subsequent phaco in eyes with FTMH and cataract. Muselier et al. reported similar visual acuity outcomes at 12 months after PPV in eyes with FTMH treated with combined PPV/phaco versus PPV and consecutive phaco surgery (0.50 ± 0.38 and 0.58 ± 0.38, respectively; $p = 0.36$) [10]. The retrospective study by Muselier et al. included an inherent bias since all patients with cataract had to be included in the combined group. In contrast, our study patients had no significant cataract at baseline and, therefore, the two groups in our study had similar baseline BCVA. The absence of significant cataract at baseline was essential for ethical randomization of patients into either group. Consistent with the study results of Muselier et al., our study also found similar improvement in BCVA after combined PPV/phaco versus PPV/deferred phaco after 12 months of follow-up. Also according to Muselier et al., there was significantly more BCVA improvement in combined PPV/phaco patients compared with PPV/deferred phaco patients at the 6-month follow-up visit. This is related to the development of cataract during this period in group 2 patients. Until month 6, just six patients had cataract surgery. Between months 6 and 12, 21 patients had cataract surgery according to protocol and this contributed for further BCVA improvement in group 2 patients. For this reason, at visits 9 and 12, no significant difference in BCVA between groups was detected. Of note, our study was not powered to detect intergroup BCVA differences smaller than 0.15 logMAR or 6 ETDRS letters. However, previous studies have shown improvement after PPV for FTMH varying from 0.30 (12 ETDRS letters) to 0.37 (15 ETDRS letters) logMAR [14, 15], values much higher than 0.15 logMAR or 6 ETDRS letters. Thus, the expected change in BCVA is much higher than the difference that could be detected with the sample size of the current study.

In the present study, there was a myopic shift in both groups that started 1 month after surgery: considering the absolute values of the spherical equivalent (graphic 3), the mean shift from baseline to 1 month after surgery was 1.68 and 1.19 diopters, in groups 1 and 2, respectively. In the PPV/phaco group, this shift was expected and induced by the placement of an intraocular lens, which power was calculated for an expected refraction of − 0.5 spherical diopters. In the PPV-deferred phaco group, this myopic shift early after PPV maybe be related to PPV-induced lens refractive changes, as reported by Muto et al. [16]. Kawakubo et al. described similar myopia progression (-2.11 ± 1.89 D) after lens-sparing vitrectomy for macular holes [17]. Later in our study, especially in the last 6 months of follow-up, a great majority of group 2 patients underwent phacoemulsification surgery, and the myopic shift was mostly secondary to IOL insertion focusing a − 0.5 spheric diopters refraction. Considering the difference between the spherical equivalent and predicted refraction, there was no difference between groups. Hamoudi et al. also did not verify a significant difference between refractive outcomes when comparing combined PPV/phacoversus sequential surgery for epiretinal membranes [18].

The current study is also the first prospective study to compare the macular sensitivity threshold following combined PPV/phaco versus PPV/deferred phaco in phakic eyes with FTMH and no significant cataract. A gradual 3–3.5-dB increase in mean macular sensitivity threshold was observed in both groups during the 1-year post-PPV study follow-up period; the improvement in macular sensitivity from baseline to 12 months was significant in both groups. Similarly, Richter-Mueksch et al. reported a significant 2-dB improvement in macular sensitivity threshold in the 8° central macular grid after PPV or combined PPV/phaco in eyes with FTMH or ERM and cataract at 1-year post-PPV [19]. The 6° expert examination protocol of the MAIA microperimeter analyzes an area of retina (~ 6 mm) much larger than the area affected by a MH (~ 1 mm). Thus, if we had microperimetry which focuses on the central 1° of the macula, that may be better suited than the 6-degree expert examination protocol to detect significant improvements in macular sensitivity following FTMH surgery. The significant increase in macular sensitivity in the current study observed at 12 months compared with baseline supports the safety of both interventions, since macular sensitivity is a measure of retinal function. Finally, in future studies, it would be interesting to compare the macular sensitivity threshold of closed macular holes with the fellow normal eye (in cases of unilateral FTMH).

In the present study, the FTMH closure rate at 12 months after one PPV was similar in both groups (73% and 75% in groups 1 and 2, respectively). The rate of successful FTMH closure has increased over the last two decades, ranging from 58% in 1991 [20] to 78–100% in more recent studies [14, 15, 18]. Of note, 69% of patients with FTMH in the present study had stage 3 or 4 FTMH and, 29.4% and 30.3% had a minimum linear diameter greater than 600 μm, with chronic symptoms. In fact, patients have difficulty in accessing our public health network and some arrive months after the initial symptoms. Also, only one vitrectomy surgery was performed in each patient since none of them accepted a second surgery based on the uncertainty of obtaining a good ILM flap for macular hole tamponade (the original ILM peeling was usually performed using a large extension of ILM around the FTMH) and also due to the risk of retinal detachment; this may explain the 73–75% FTMH closure rates observed in our study.

Two patients from group I had posterior iris synechiae. This adverse event maybe related to a higher postoperative inflammation associated to the combined procedure. In fact, Wensheng et al. verified 6.9% rate of segmental synechiae of the iris to the anterior capsule after combined surgery for vitreoretinal diseases [21]. To prevent this complication, frequent steroid drops (five times a day) for the first postoperative week is a very important measure. Also in the PPV/phaco group, there was 1 patient with a tilted IOL. This complication may be related to a larger capsulorhexis, which sometimes allows a partial drop out of the IOL border from the capsular bag. A uniform capsulorhexis that completely overlies the IOL optic area is also a very important measure to avoid postoperative tilt. In the PPV/deferred phaco group, two patients had the IOL positioned in the ciliary sulcus due to intraoperative posterior capsular rupture. One explanation for this complication would be the increased instability of the anterior chamber and the posterior capsule in vitrectomized patients during phacoemulsification surgery. To avoid this complication, surgeon can decrease the flow rate and the balanced salt solution infusion pressure.

The present study has important limitations. The small sample size allows us to detect only differences in BCVA higher than 1.5 LogMAR. Additional studies with larger sample sizes are needed to confirm our preliminary findings. Ideally only one surgeon, instead of 2, would be more reasonable considering the best methodology standards. It would lead to more uniform results, but this was not possible due to logistic problems. Finally, a better design of the microperimetry analysis would yield more profitable and useful data.

In summary, among patients with FTMH and no significant cataract at baseline, combined PPV/phaco was associated with similar BCVA, microperimetry, and FTMH closure outcomes at 1 year when compared with PPV/deferred phaco.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the (Comitê de Ética em Pesquisa do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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