Evaluation of the Efficacy of Pneumatic Vitreolysis Treatment for Symptomatic Vitreomacular Traction Syndrome

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ABSTRACT

Purpose: To evaluate the posterior vitreous release rates after a single injection of expansile gas in patients with focal vitreomacular traction (VMT) syndrome.

Materials and Methods: Thirteen eyes of 13 consecutive patients with focal symptomatic VMT were reviewed retrospectively. Intravitreal injection of 0.3 mL of pure perfluoropropane (C3F8) was performed. Patients were instructed to bob their head forwards and backwards similar to the head movements of a 'drinking bird' until VMT release. A full ophthalmic examination and optical coherence tomography (OCT) was performed at each visit.

Results: The mean age of the patients was 66.23±10.01. Seven patients (53.8%) were female, and 6 patients (46.2%) were male. VMT was released in 12 patients (93.7%), and the mean release time was 7.58 days (1-14 days). In two eyes (15.4%) with VMT associated with the full thickness macular hole (FTMH), the macular hole was not closed despite the posterior hyaloid release. The mean pre-treatment best-corrected visual acuity (BCVA) improved significantly from 0.71±0.34 LogMAR to 0.54±0.28 LogMAR after the treatment (p=0.045). The mean central macular thickness (CMT) decreased significantly from 338.46±65.00 µm to 282.77±62.26 µm (p=0.013). In the preoperative period, the mean horizontal length of vitreomacular adhesion (HLVMA) was 691.92±268.24 µm. No correlation was found between HLVMA and release time (p=0.828). No complications were observed.

Conclusions: Pneumatic vitreolysis is a relatively safe, minimally invasive and effective treatment option for symptomatic focal VMT syndrome.

Keywords: perfluoropropane; pneumatic vitreolysis, vitreomacular traction.

INTRODUCTION

Incomplete separation of the posterior hyaloid membrane from areas where it is tightly adhered to the internal limiting membrane is called incomplete posterior vitreous detachment (PVD).[1] Vitreomacular traction (VMT) is a condition characterized by traction in the macular region that develops due to incomplete PVD in the macular region and is typically detected in the 45-65 age range.[2, 3] Patients with VMT present with symptoms of decreased visual acuity and metamorphosia as a result of the traction disrupting the foveal contour.[4] VMT is classified according to the presence of accompanying macular pathology, such as a full-thickness macular hole (FTMH), diabetic macular edema (DME), and epiretinal membrane (ERM) (isolated or not) or the diameter of the adhesion area (focal ≤1500 µm and broad >1500 µm).[5]

VMT treatment varies depending on the severity of the traction and the symptoms of the patients. As the rate of spontaneous relief in VMT cases is 30%-40%, observation can be considered as a treatment option in asymptomatic cases.[6-9] However, the fact that a high risk of developing FTMH and ERM due to VMT has been found in various studies.[4, 10]] has caused retinal surgeons to turn to alternative treatment options other than observation. Pars plana vitrectomy (PPV), pharmacological vitreolysis with ocriplasmin (Jetrea; Thrombogenics, Leuven, Belgium) and pneumatic vitreolysis (PVL) are among the alternative treatment methods. Although PPV is the most effective

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method in the treatment of VMT, it is invasive, expensive and carries the risk of retinal tears, cataract formation and endophthalmitis.[11, 12]

After the results of the Trial of Microplasmin Intravitreal Injection for Non-surgical Treatment of Focal Vitreomacular Adhesion (The- MIVI-TRUST Trial).[13]] were published in 2012, the Food and Drug Administration (FDA) approved the use of ocriplasmin treatment in isolated or VMT cases associated with FTMH. Ocriplasmin treatment, which is a less invasive treatment method compared to PPV, has been shown to have a success rate of 26.5%.[13] In addition, the success rate of ocriplasmin treatment in VMT cases without ERM has reportedly increased to 40%.[14] However, in the following years, the high cost of ocriplasmin treatment and the possible side effects, such as temporary vision loss, dyschromatopsia, zonulolysis, disruption of the ellipsoid zone in optical coherence tomography (OCT) and electroretinographic changes, prevented the widespread use of this new treatment method.[15-18] Therefore, more effective, cheaper and safer treatment methods have begun to be investigated to treat VMT.

In the study by Chan et al. published in 1995.[19]], the PVL technique was defined for the first time, and its effectiveness in treating stage 1-2 macular holes was demonstrated. The authors reported that after a 0.3 cc perfluoropropane (C3F8) gas injection, complete PVD developed 96% and stage 2 macular holes were 57% closed. In subsequent studies.[18, 20]], it was shown that PVL treatment resolves VMT by 80% in isolated VMT eyes. Other studies reported that the application of the postoperative 'drinking bird' maneuverer and the use of long-acting gas such as C3F8 increase the effectiveness of PVL treatment.[21, 22] PVL therapy is increasingly used in the treatment of VMT due to its high efficacy, minimal side effects and easy application. In the present study, we aimed to investigate the effectiveness and safety of PVL treatment in patients with focal symptomatic VMT syndrome.

MATERIALS AND METHODS

This retrospective, consecutive case series was conducted with patients who underwent PVL treatment due to symptomatic focal VMT between January 2018 and February 2020 in the retina unit of our clinic. Patients with a dense cataract that prevents OCT measurement, aphakia, broad VMT, high myopia (> -4.0 diopter), a history of any previous retinal surgery or glaucoma were excluded. Patients who did not have a follow-up period of at least 3 months after PVL treatment were also excluded from the study. All patients were informed about the treatment and the potential complications. Informed consent was obtained preoperatively from all patients. The study procedures were approved by the institutional review board of the hospital and adhered to the tenets of the Declaration of Helsinki. The study protocol was approved by the local ethics committee.

Detailed ophthalmologic examinations of the patients were performed before and after the PVL treatment by the same experienced ophthalmologist (AK). Best-corrected visual acuity (BCVA) was measured using a Snellen chart and transformed into a 'logarithm of minimum angle of resolution (LogMAR)' scale. All cases were assessed for the presence of VMT using OCT (Cirrus HD 5000, Carl Zeiss Meditec AG, Jena, Germany) and the 'HD Cross' analysis programme. Horizontal length of vitreomacular adhesion (HLVMA) values were measured manually. Focal VMT cases (diameter of the adhesion area ≤ 1500 µm) were selected according to the classification defined by the International Vitreomacular Traction Study Group.[5] Diameter of FTMH values were measured manually. Central macular thickness (CMT) values were measured using the Macular Cube analysis programme. The patients were followed up daily in the first week, and repeated examinations were performed in the second week, the first month, the second month and the third month after the PVL treatment. The frequency and time of VMT release, BCVA values and CMT values were compared within the preoperative and postoperative periods, and complications due to PVL treatment were analysed.

Pneumatic vitreolysis technique

All PVL applications were performed under sterile conditions by the same surgeon (SAO). All patients were given 500 mg oral acetazolamide (Diazomid, Sanofi-Aventis, Longjumeau, France) 2 hours before PVL treatment to prevent increased IOP due to intravitreal gas injection. Next, 5% proparacaine hydrochloride (Alcaine, Alcon Pharmaceuticals Plc, Fort Worth, Texas, US) was applied to provide topical anaesthesia. Subsequently, 10% povidone iodine antiseptic solution was used to clean the eyelashes, eyelids and periorbital tissues. To prevent endophthalmitis, 5% povidone iodine solution was applied to the conjunctiva and fornix surface for 2 minutes. Next, 0.3 cc pure C3F8 gas was injected intravitreally at the inferotemporal quadrant 4 mm behind the limbus. After the gas injection, pressure was applied to the scleral entry with a cotton-tipped applicator. Limbal paracentesis was performed in all patients to reduce intraocular pressure (IOP) after the gas injection. At the end of the application, central retinal artery perfusion was checked in all patients. The patients were told that they should do the 'drinking bird' head movement 20 times every half hour for 2 weeks postoperatively. In the postoperative period, 0.5% topical moxifloxacin (Vigamox, Alcon Pharmaceuticals Plc, Fort

Worth, TX, US) and 1% topical prednisolone acetate (Pred-forte, Allergan, Dublin, IRL) was applied four times daily for 2 weeks.

Statistical analysis

The "Statistical Package for Social Sciences version 25.0 for Windows" was used for statistical analysis. Prior to performing calculations on the non-qualitative data, the Kolmogorov-Smirnov test was used to determine the conformity of the data with normal distribution. For parametric and non-parametric variables, a paired t-test and a Wilcoxon signed rank test were respectively used. A Pearson correlation test was used to assess the relationship between the numeric variables. A p value less than 0.05 was accepted as statistically significant.

RESULTS

A total of 13 eyes of 13 patients were included in this study. Table 1 shows the individual characteristics and findings for all cases. The mean age of the patients was 66.23±10.01 years (range 47-77 years). Seven patients (53.8%) were female, and 6 patients (46.2%) were male. In the preoperative period, 10 eyes (76.9%) were phakic, and 3 eyes (23.1%) were pseudophakic. VMT was released in 12 patients (93.7%), and mean release time was 7.58 days (range 1-14 days) (Figure 1). Releasing of the posterior hyaloid could not be achieved in 1 eye (6.3%) with PVL treatment. In this eye, HLVMA was 1338 µm, and ERM and VMT were present. The mean follow-up period of patients after PVL treatment was 5.92±2.81 months (range 3-10 months). In 2 eyes (15.4%) with VMT associated with the FTMH, the macular hole was not closed despite the posterior hyaloid release. In the first patient, the baseline

Table 1: *Findings for all patients before and after the pneumatic vitreolysis treatment.*

Patient Number	Sex	Age	Eye	Lens status	Additional diagnosis	Diagnosis	Pre-treatment VA (LogMAR)	Pre-treatment CMT	Pre-treatment HLVMA	Gas used	VMT release	Release time (days)	Follow-up time (months)	Post-treatment VA (LogMAR)	Post-treatment CMT	Adverse effect
1	M	77	OD	Phakic	DME	VMT	0.5	380	672	C3F8	Yes	7	4	0.7	197	None
2	M	62	OD	Pseudophakic	DME	VMT	0.7	352	709	C3F8	Yes	1	4	0.6	327	None
3	F	76	OD	Phakic	DME	VMT	1.3	255	849	C3F8	Yes	8	10	1.0	287	None
4	M	47	OD	Phakic	DME,ERM	VMT	0.7	299	520	C3F8	Yes	10	8	0.4	248	None
5	F	70	OD	Phakic	None	Small FTMH with VMT	0.5	400	829	C3F8	Yes	14	10	0.5	340	None
6	F	67	OD	Phakic	None	VMT	1.0	311	700	C3F8	Yes	5	4	0.4	300	None
7	M	60	OS	Pseudophakic	DME	VMT	1.0	362	680	C3F8	Yes	9	10	1.0	355	None
8	F	77	OD	Phakic	None	Small FTMH with VMT	1.3	350	859	C3F8	Yes	7	5	0.6	206	None
9	F	76	OS	Phakic	None	VMT	0.3	223	540	C3F8	Yes	8	3	0.2	222	None
10	F	62	OD	Phakic	None	VMT	0.4	307	589	C3F8	Yes	8	4	0.0	228	None
11	M	49	OS	Pseudophakic	DME,ERM	VMT	0.6	311	370	C3F8	Yes	7	4	0.6	348	None
12	M	71	OD	Phakic	DME,ERM	VMT	0.3	375	1338	C3F8	No	-	8	0.4	242	None
13	F	67	OD	Phakic	PCV	VMT	0.7	475	300	C3F8	Yes	7	3	0.7	376	None

VA: Visual acuity, CMT: Central macular thickness, HLMVA: Horizontal length of vitreomacular adherence, M: Male, F: Female, OD: Right eye, OS: Left eye, DME: Diabetic macular edema, ERM: Epiretinal membrane, PCV: Polipoidal choroidal vasculopathy, VMT: Vitreomacular traction, FTMH: Full thickness macular hole

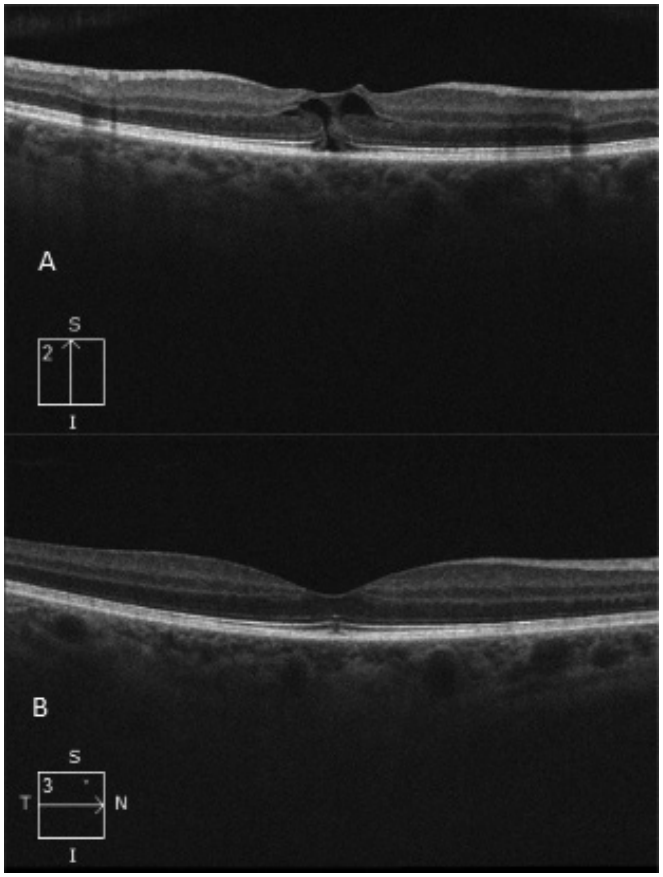

Figure 1: *İsolated vitreomacular traction syndrome in the left eye of a 76-year-old female patient (Patient 9)* **(A)**. *Optical coherence tomography (OCT) image shows release of the posterior hyaloid after pneumatic vitreolysis treatment* **(B)**.

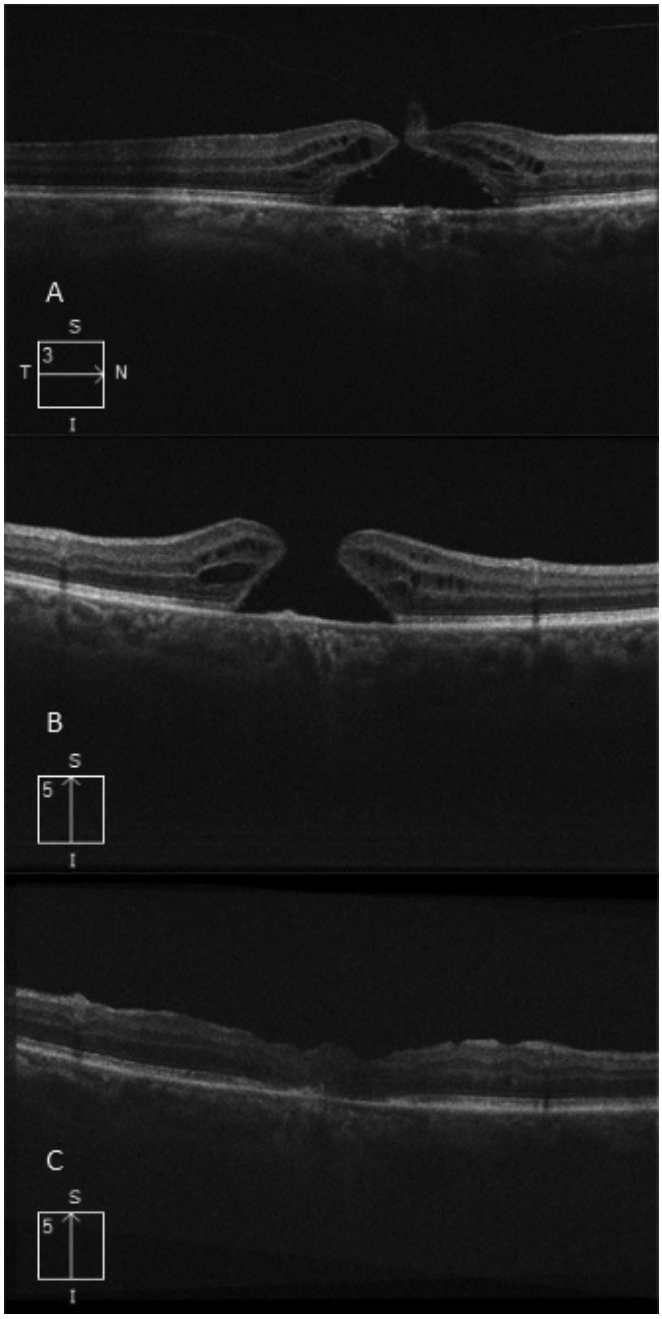

Figure 2: *Vitreomacular traction syndrome associated with small full thickness macular hole (FTMH) (130 µm) in the right eye of a 70-year-old female patient (Patient 5)* **(A)**. *Optical coherence tomography (OCT) image shows complete release of the posterior hyaloid after pneumatic vitreolysis treatment, but FTMH persists (450 µm)* **(B)**. *OCT image shows FTMH closure after pars plana vitrectomy surgery* **(C)**.

diameter of the macular hole increased from 241 µm to 419 µm, and in the second patient the baseline diameter of the macular hole increased from 130 µm to 450 µm after the PVL treatment. In these eyes, the macular holes were closed with PPV surgery (Figure 2). In addition to VMT, there was polipoidal choroidal vasculopathy (PCV) in 1 eye (6.3%), ERM in 3 eyes (23.1%) and DME in 7 eyes (53.8%) (Figure 3). The mean pre-treatment BCVA improved from 0.71±0.34 LogMAR to 0.54±0.28 LogMAR after the treatment, and the increase was statistically significant (p=0.045). After the PVL treatment, mean CMT decreased significantly from 338.46±65.00 µm to 282.77±62.26 µm (p=0.013). In the preoperative period, mean HLVMA was 691.92±268.24 µm (range 300-1338 µm). No correlation was found between HLVMA and release time (r=o.101 and p=0.755). No complications were observed due to PVL treatment.

DISCUSSION

VMT is defined as a pathology that causes deterioration in the structure of the perifoveal region and visual disturbances as a result of the traction of the posterior hyaloid.[5] Common approaches used in treating VMT are observation, intravitreal ocriplasmin injection and PPV surgery.[20, 23] It has been reported that spontaneous separation may occur in 30%-40% of eyes with focal VMT.[9, 20] However, the observation period is uncertain, and waiting for a long time for spontaneous separation may lead to the development of ERM, FTMH and vision loss.[24,

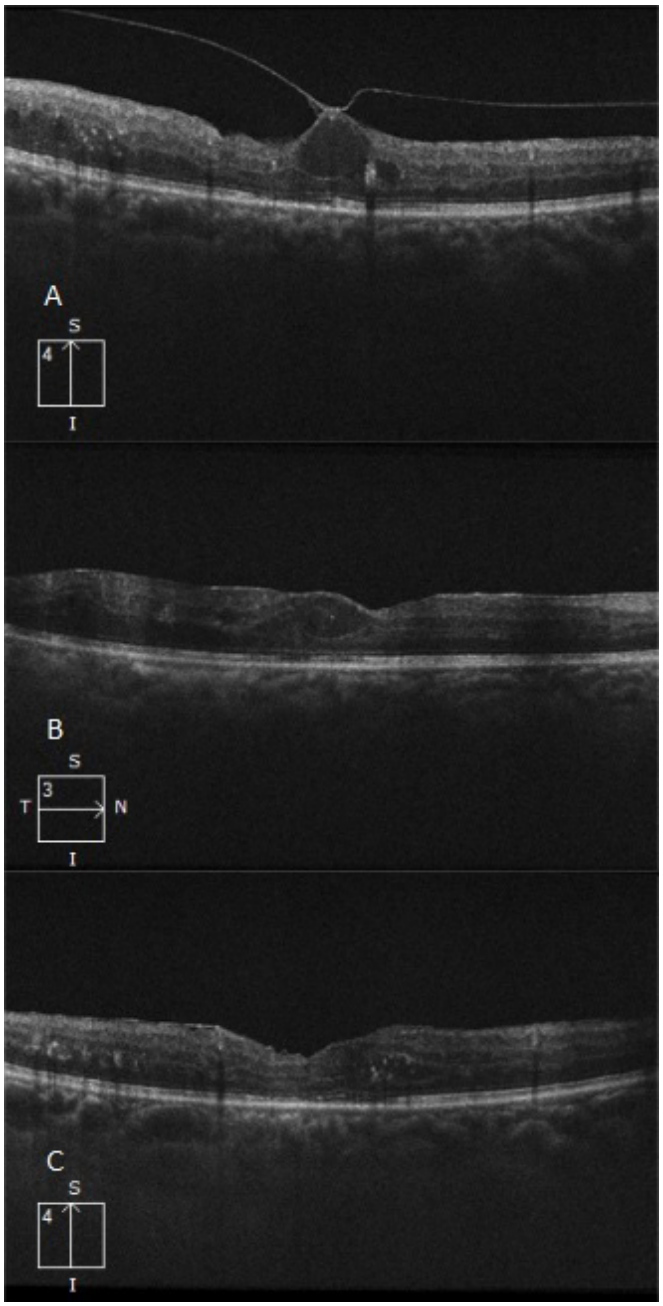

Figure 3: *Vitreomacular traction syndrome associated with diabetic macular edema resistant to intravitreal ranibizumab and dexamethasone implant treatment in the right eye of a 47-year-old male patient (Patient 4)* **(A)**. *Optical coherence tomography (OCT) image shows release of the posterior hyaloid and reduction of macular edema after pneumatic vitreolysis (PVL) treatment* **(B)**. *OCT image shows that the single dose intravitreal ranibizumab injection administered after PVL treatment completely regressed diabetic macular edema* **(C)**.

[25] Intravitreal ocriplasmin is a recombinant protease that removes vitreoretinal adhesions by dissolving the protein matrix at the vitreoretinal interface.[13, 26] The relatively low efficacy rate of ocriplasmin treatment (40%), its effectiveness in a limited patient group, its high cost and its serious side effects are the factors that limit its widespread use.[15-18] PPV is the most effective method in treating VMT, and the success rate is approximately 98%.[27] However, PPV surgery requires surgical experience and additional local or general anaesthesia. It is also an invasive and expensive treatment that carries the risk of retinal tears, cataract formation and endophthalmitis.[11, 12]

In the study by Chan et al. published in 1995.[19]], the PVL technique was defined for the first time, and its effectiveness in treating stage 1-2 macular holes was demonstrated. The authors reported that after 0.3 cc of C3F8 gas injection, complete PVD developed 96% and stage 2 macular holes were closed by 57%. In the study by Mori et al. published in 2007.[28]], the authors reported that after 0.5 cc sulphur hexafluoride (SF6) gas injection, the VMT was released by 95% in a prone position for 3-5 days. They reported the VMT release time as being 2 weeks on average. Rodrigues et al..[29]] reported the VMT release rate as 40% in the first month after 0.3 cc of C3F8 gas injection. However, they reported that the treatment success rate increased to 60% by postoperative month six. Rodrigues et al..[29]] did not recommend any postoperative positioning to their patients. Steinle et al..[21]] reported the VMT release rate as 84% after 0.3 cc of C3F8 gas injection. They recommended the 'drinking bird' movements to their patients in the postoperative period, and the VMT release time was reported to be 13 days on average. The study by Chan et al..[18]] evaluating the effect of PVL treatment on VMT has the most cases. In their study, after the injection of 0.3 cc C3F8 gas patients were advised to avoid the supine position in the postoperative period. The authors found that VMT was released in 43 of 50 eyes (86%) after a mean of 3 weeks. Cokl et al.[30]] compared the efficiency of both gases and reported a success rate of 21.4% in the SF6 group, while the VMT release rate was 62% after C3F8 gas injection. Özdemir et al.[22]] compared the efficiency of SF6 and C3F8 gases in relation to VMT release and reported a 100% success rate in both groups. They believed their high success rates and short release time were related to the postoperative 'drinking bird' position.

In the present study, we applied 0.3 cc of C3F8 gas in all the cases. We determined the effectiveness of PVL treatment as 93.7% with a mean release time of 7.58 days. Although it is unknown exactly how the intravitreally injected gas causes the releasing of the posterior hyaloid, it is believed that intravitreal gas increases the liquefaction of the vitreous and that with bobbing head movements a tear develops in the posterior vitreous cortex and the liquefied vitreous passes through it, causing PVD.[19, 22] In addition, it is thought that long-acting gases may induce PVD more by further increasing the vitreous liquefaction.[18] We believe the high success rates and short release time we achieved

in our study were related to both the use of long-acting gas and the post-treatment 'drinking bird' movements. In the present study, the induction of PVD could not be achieved in 1 eye (6.3%) with PVL treatment. In this eye, HLVMA was 1338 µm, and ERM and VMT were present. Rodrigues et al.[29] reported HLVMA over 750 µm as an absolute failure criteria for PVL therapy. In addition, it has been shown that patients with HLVMA below 500 µm respond well to PVL treatment.[21, 22, 29] We believe this situation in only the one eye in which we could not obtain PVD with PVL treatment is due to the high HLVMA. In our study, the mean pre-treatment HLVMA was 691.92±268.24 µm. Our mean HLVMA was higher than that in the other studies in the literature. In addition, PVL treatment was successful in 3 eyes, although the HLVMA was over 750 µm. Chan et al.[18] reported that in the presence of ERM, the success rate of PVL treatment decreased to 50%, and in the presence of diabetes mellitus it decreased to 25%. Another study.[29] found that the presence of ERM reduces the VMT release rate. In the present study, there were ERMs in 3 eyes (23.1%) and DME in 7 eyes (53.8%). We obtained high rates of VMT release and a significant increase in BCVA values with PVL treatment despite high rates of concurrent macular pathologies. In our study, VMT complicates the treatment of DME, and macular edema regresses with the elimination of antero-posterior traction. We believe the response to intravitreal anti-vascular endothelial growth factor drugs or intravitreal dexamethasone implant treatment may increase in DME following the release of the vitreous.

PVL treatment can result in the closure of small macular holes associated with VMT. Chan et al.[18] reported a 53% macular hole closure rate and 100% vitreous release with C3F8 gas injection in small FTMH with a diameter less than 250 µm accompanied by VMT. Mori et al. [28] achieved 50% closure of stage 2 macular holes and 95% vitreous release with SF6 gas injection in a prone position for 3-5 days. The same study achieved 100% success for FTMHs with a diameter less than 200 µm. Özdemir et al.[22] reported that the posterior vitreous was released with PVL treatment in 2 eyes with small FTMHs, but the macular holes were not closed. In our study, we found that although the posterior vitreous was released with PVL treatment in 2 eyes with small FTMHs with VMT, the macular holes were not closed. Although the diameter of the macular hole in one of the eyes was less than 200 µm, closure could not be achieved with PVL treatment. Furthermore, we observed that the diameter of the macular holes enlarged after the PVL treatment. PPV surgery was then performed on these eyes, and the macular holes were successfully closed.

It has been reported in the literature that low rates of retinal tears and retinal detachment may develop after PVL treatment.[20, 22, 23] It has been stated that the risk of developing retinal tears is high in highly myopic eyes and that it is appropriate to avoid PVL treatment in these eyes.[22, 23] Because we did not include highly myopic eyes in our study, we did not detect any retinal tears or retinal detachment after PVL treatment. No other complications were observed in the present study.

There are some limitations to this study, such as the small number of patients, the lack of subgroup analysis and the retrospective nature of the study, all of which limit our comparisons. However, we found that PVL treatment is an effective, safe, cheap and easily applicable method to treat isolated or concurrent focal VMT cases. PVL therapy can be used as the first choice of treatment for focal symptomatic VMT. However, further prospective studies with a greater number of patients are needed.

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