

Pneumatic Vitreolysis for Management of Symptomatic Focal Vitreomacular Traction

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Abstract

Pneumatic vitreolysis (PVL) is the intravitreal injection of a small quantity of expansile gas for the purpose of achieving focal vitreomacular traction (VMT) release for eyes with symptomatic VMT, or inducing VMT release and closure of the macular defect for eyes with a small stage-2 macular hole (MH). Initially, there was limited interest in this technique upon its introduction for clinical treatment in human eyes in 1993. With the advent of optical coherence tomography allowing detailed observation of vitreomacular interface changes and rising importance of medical economics in recent years, there has been increasing interest in PVL, a low-cost procedure for managing symptomatic VMT. The success rates of VMT release in the literature have ranged from 60% to 100% and the rates of closure of small macular holes have ranged from 50% to 80% following PVL. In a recent retrospective consecutive series of 56 eyes in two centers undergoing C3F8 gas injection, Chan and Mein reported an overall success of 86% in VMT release and 60% closure of small macular holes with few adverse events (7% with retinal breaks, retinal detachment, or progression of VMT). Multiple recent studies have shown superior outcome utilizing C3F8 gas compared with SF6 gas for PVL. In conclusion, PVL is a promising, low-cost therapeutic option, with the potential for managing symptomatic focal VMT on a global scale.

Keywords: Gas Injection; Ocriplasmin; Pneumatic Vitreolysis; Vitreomacular Adhesion; Vitreomacular Traction

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BACKGROUND

Vitreoretinal disorders refer to a spectrum of interactions between the posterior hyaloid and the underlying retinal surface, ranging from innocuous attachment to substantial disruption of the retinal integrity. Such an

interaction assumes particular clinical relevance when the macula is affected, given its potential visual impact. Vitreomacular disorders are generally divided into two broad categories: vitreomacular adhesion (VMA) and vitreomacular traction (VMT).^[1,2] The former is defined as posterior vitreomacular attachment without disruption of the macular integrity, while the latter is defined as posterior vitreomacular attachment with tractional distortion of the perifoveal architecture inducing visual disturbance.^[1,2] VMA and VMT can occur in isolation, or they can develop in conjunction with comorbid macular conditions, i.e., macular holes, macular edema, and

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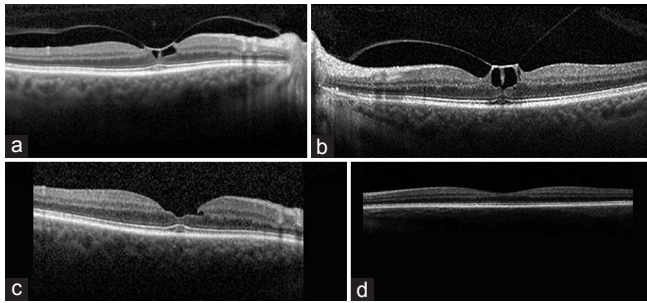


Figure 1. (VMT-only). A 70 year-old pseudophakic woman presented with bilateral symptomatic vitreomacular traction (VMT) within one disc area in size, both eyes in March 2016. There was mild eccentric epiretinal cellophane maculopathy, right eye (a), and an outer foveal defect, left eye (b). She underwent pneumatic vitreolysis (PVL), right eye on March 2, 2016 and VMT release developed 3 weeks later (c). She also underwent PVL, left eye on April 19, 2016 with achievement of VMT release 6 days later (d). The BSCVA was improved to 20/30 for each eye.

epiretinal membrane.^[2] In addition, they can be linked to other disease entities, such as diabetic retinopathy, retinal vascular disorders, and age-related macular degeneration. It has been estimated that approximately 1.5% of the general population is affected by eye diseases associated with VMA.^[3] The prevalence of VMT syndrome is 22.5 per 100,000 in the United States. Its annual incidence is 0.6 per 100,000.^[3]

One study involving three major referral eye centers showed that 14.74% of their retina clinic patients were found to have VMA (12.39% unilateral and 2.36% bilateral).^[4]

Treatment Options for VMT

Observation and pars plana vitrectomy

Conventional management options for VMT with or without a small macular hole include observation, intraocular injection of ocriplasmin, and vitrectomy. Observation is a viable option as 30-40% of VMTs may resolve on a spontaneous basis,^[5-10] although its timing is unpredictable and an extended waiting period may be required before its occurrence. Although vitrectomy has the potential of resolving VMT and closing macular holes over 90% of the time, it is an invasive procedure associated with substantial cost and potential morbidities, even in this modern era of small-gauge microsurgery. In addition, a randomized controlled clinical trial conducted by de Bustros et al in 1994 studied vitrectomy in eyes with symptomatic impending macular holes associated with fellow eyes with stage-3 or 4 macular holes for prevention of full-thickness macular holes, and the results were inconclusive.^[11] Therefore, vitrectomy is reserved for VMT cases with more advanced symptoms and worse visual acuities,

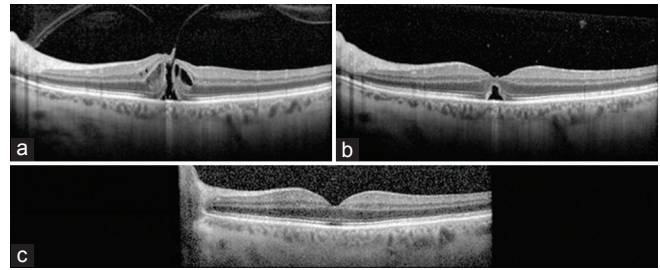


Figure 2. (VMT with small stage-2 macular hole). A 71 year-old phakic man presented on Feb 9, 2016 with vision loss due to a narrow stage-2 macular hole associated with overlying focal VMT with an elevated retinal flap, left eye (a). His BSCVA was decreased to 20/150, left eye. After an extensive discussion of therapeutic options including a vitrectomy, ocriplasmin, or PVL, he decided on PVL. VMT release was achieved at one week after PVL, and macular hole closure started after 4 days of partial face-down positioning (b). Complete macular hole closure with VA recovery to 20/30 was noted at 6 weeks after PVL (c).

and its role for managing less severe cases of VMT is questionable.

Ocriplasmin

The FDA approved the clinical use of ocriplasmin for VMT with or without macular holes in 2012, after the completion of the Trial of Microplasmin Intravitreal Injection for Non-surgical Treatment of Focal Vitreomacular Adhesion (The MIVI-TRUST Trial).^[12] The published report of the MIVI-TRUST Trial showed successful release of VMT in 26.5% of the treated eyes and 10.1% of the placebo eyes.^[12] Subgroup analysis showed that the success rate was increased to 40% for eyes without cellophane maculopathy, and to 60% for small macular holes of <250 microns. The Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Inducing Macular Hole (OASIS) Trial reported successful VMT release in 41.7% of affected eyes in the ocriplasmin group and 6.2% in the placebo group over 2 years.^[13] In 2016, Lim et al reported in the Macula Society Collaborative Retrospective Study a rate of 45% for release of VMT and a rate of 40% for MH closure associated with ocriplasmin for eyes with VMT.^[14]

In recent years, there have been a series of anecdotal reports of significant ocular complications associated with intraocular administration of ocriplasmin, including transient visual loss, persistent dyschromatopsia, electroretinographic changes, subluxation of the crystalline lens related to zonulolysis, and disturbance or dehiscence of the ellipsoid layer documented by ocular coherence tomography (OCT).^[15-19] These adverse events have created major concerns among many retinal surgeons in the clinical use of this drug despite its FDA approval status. In response to such concerns, ThromboGenics Inc, the manufacturer of ocriplasmin completed a post-marketing survey (ORBIT) on the

clinical use of ocriplasmin among ophthalmologists in the US, which showed limited rates of adverse events associated with ocriplasmin in the treatment of VMT and closure of small macular holes in the US (2017 ARVO, unpublished data).

However, the high cost of ocriplasmin and its limited efficacy remain to be substantial hurdles hindering the widespread usage of ocriplasmin for vitreoretinal disorders in the US.

Pneumatic Vitreolysis

Chan first introduced pneumatic vitreolysis (intravitreal injection of a small quantity of expansile gas for resolving VMT) and closure of small macular holes in 1993.^[20] This initial pilot study published in 1995 reported the achievement of VMT release in 96% of the treated eyes and closure of 57% of small stage-2 macular holes following intravitreal injection of 0.3 mL of perfluoropropane (C3F8) gas. In 2001 and 2006, Costa et al and also Jorge et al reported 100% VMT release and closure of 83% of stage-2 macular holes in a small series of eyes receiving pure C3F8 gas.^[21,22] In 2007, Mori et al reported VMT release and closure of stage-2 macular holes after injection of pure SF₆ gas followed by 3 to 5 days of face-down positioning.^[23] They were successful in inducing VMT release in 95% of their case series (19 of 20 eyes), and closure 50% of the of stage-2 macular holes. For the subset of eyes with VA better than 20/40 and size of macular holes of less than 200 microns, the success of macular hole closure was 100%. In their case series in 2013, Rodrigues et al showed resolution of VMT in 40% of treated eyes at one month after injection of 100% C3F8 gas, and another 20% was shown to develop the same by 6 months in a case series of 15 eyes.^[24] Given the low cost and convenience of gas injection as well as a low rate of adverse events reported in prior retrospective studies, PVL may serve as an alternative to the much more costly treatment with ocriplasmin or vitrectomy for managing VMT.

Recently, Steinle et al in a retrospective study, reported a success rate of 84% with C₃F₈ gas for resolving VMT.^[25] In a separate presentation, the same authors reported 84% success with C3F8 gas, 56% with SF₆ gas, and 48% with ocriplasmin in release of VMT in a comparative retrospective case series for treatment of VMT syndrome (N Steinle et al, unpublished data, ARVO 2016, Seattle, May 2, 2016). In 2016, Day et al published a success rate of 55.6% utilizing SF₆ gas in releasing VMT in a retrospective case series of 9 eyes.^[26] In a recent retrospective study on 50 consecutive eyes in 2 centers, Chan and Mein et al reported an overall success of 86% in VMT release (80% in VMT-only eyes and 100% in small stage-2 MH [≤ 250 microns]).^[27] In 2017, Claus et al reported 84% (16 of 19 eyes) success of VMT release utilizing a single injection of 0.2 mL of C2F6 gas.^[28] Thus,

multiple retrospective studies have shown a superior outcome utilizing a long-acting gas in comparison to a short-acting gas for PVL.

Technique of PVL

After obtaining an informed consent, topical 0.5% proparacaine followed by subconjunctival injection of 2.0% lidocaine hydrochloride with or without 0.5% bupivacaine hydrochloride is administered for the operated eye.^[20,27] Sterile prepping with Betadine is then performed. Subsequently, prophylactic paracentesis to remove 0.1 ml to 0.2 ml of aqueous is usually performed with a short 27- or 30-gauge needle connected to a tuberculin syringe via the limbus. Next, 0.3 ml of filtered perfluoropropane (C3F8) gas is injected through a short-30-gauge needle at the pars plana into the vitreous cavity. The intraocular pressure is measured and the central retinal arterial perfusion is monitored. If necessary, ocular hypotensive medications are prescribed, with or without additional anterior chamber paracentesis, to normalize the intraocular pressure and ensure appropriate central retinal arterial perfusion before discharging the patient. All treated patients are asked to avoid supine position, until resolution of the intraocular gas. Treated patients with an advanced impending macular hole or stage-2 macular holes are required to maintain face-down position as much as possible for at least four days. Treated patients are monitored closely afterwards, i.e. within 24 hours after gas injection, and weekly subsequently. Treated patients are asked to apply topical antibiotic and corticosteroid in combination or separately for a week or longer.

PVL in Patients with VMT

A consecutive series of 55 patients (56 eyes) with symptomatic VMT with or without small stage-2 macular holes (≤ 250 microns) underwent PVL in two centers (Southern California Desert Retina Consultants and Retinal Consultants of San Antonio) from 2010 to 2016. There were 40 women and 15 men. Release of VMT was achieved in 48 eyes (85.7%) at a mean of 3.1 weeks (range: 5 days to 9 weeks) after a single intraocular C3F8 gas injection. For eyes with VMT only, VMT release was achieved in 29 of 36 eyes (80.6%), For eyes with small stage-2 macular holes (within 250 microns in diameter), VMT release was attained in 19 of 20 eyes (95%), followed by closure of the associated macular hole in 15 eyes (60%). The mean follow-up time was 10.3 months. The stage-2 macular holes that did not close initially with PVL were all closed with pars plana vitrectomy subsequently. These success rates associated with PVL are higher than the published rates associated with ocriplasmin (ranging from 26.5% to 60% in VMT release).

Timing of VMT Release

As noted above, the average timing of C3F8 gas injection to VMT release associated with PVL was 3.1 weeks, but it ranged from 5 days to 9 weeks.^[27] Thus, although 84% of VMT releases developed within a month, 16% did not occur until 5 to 9 weeks after gas injection. Therefore, one should refrain from assuming failure and switching to alternate treatment prematurely, until waiting for 2 months after PVL.

Adverse Events

There were limited adverse events associated with PVL in our recently expanded retrospective series (7%). Two phakic eyes that developed a retinal flap tear responded well to barrier laser treatment with final visual acuity of 20/40 in both of these eyes. Another patient with an initial advanced impending macular hole in a phakic eye developed a full-thickness macular hole after PVL. The macular hole was successfully closed with pars plana vitrectomy, and the visual acuity recovered to 20/30. A fourth patient who initially responded to PVL with VMT release in a phakic eye despite previous failure to respond to ocriplasmin, developed a rhegmatogenous retinal detachment with a peripheral retinal break. This eye was successfully treated with a pars plana vitrectomy. The visual acuity decreased from 20/30 to 20/70 primarily due to progression of the cataract afterwards.

Subgroup Analysis to Predict Success and Failure

Regarding our recent retrospective series, subgroup analysis was performed to determine baseline factors associated with success versus failure in response to PVL.^[27] Rate of VMT release decreased to 50% in the presence of more than grade-0 cellophane maculopathy according to Gass classification (grade-0 refers to a translucent epiretinal membrane with no underlying retinal distortion), and to 25% in the presence of diabetes mellitus. Univariate analysis showed an increased rate of VMT release in eyes with VMT within 1 disc or less diameter, ($\chi^2 = 13.1$, $P = 0.002$), non-diabetic eyes ($\chi^2 = 8.8$, $P = 0.007$), and eyes with stage-2 MH, ($\chi^2 = 5.47$, $P = 0.019$). There was also a trend towards success in VMT release for patients without cellophane maculopathy of > grade 0, ($\chi^2 = 3.32$, $P = 0.068$). Further assessment with stepwise logistic regression showed younger age (mean age of 69 versus mean age of 78, $P = 0.012$), followed by better baseline best spectacle-corrected visual acuity ($P = 0.044$), absence of diabetes mellitus ($P = 0.077$), and female gender ($P = 0.045$) to be predictors of successful VMT release.

Selected Case Examples

Case 1 (VMT-only), Figure 1

A 70 year-old pseudophakic woman presented with bilateral progressive central visual deficit in early March 2016. Best-spectacle corrected visual acuity (BSCVA) was 20/40, right eye and 20/50, left eye. Fundus examination revealed focal VMT within 1 disc area in size in both eyes. There was also mild eccentric epiretinal cellophane membrane in the right eye (1a). Notice a vertical slit of outer foveal defect had developed in the left eye by 4/19/2016 (1b). After discussion of management options, she decided to undergo PVL, which was performed for her right eye on 3/2/2016 and resulted in VMT release within 3 weeks after PVL (1c). On 4/19/2016, she underwent PVL for her left eye as well. VMT release was achieved for her left eye 6 days later (1d). At 6 months after PVL, the BSCVA improved to 20/30, right eye, and 20/30, left eye.

Case 2 (Small stage-2 macular hole), Figure 2

A 72 year-old phakic man complained of central vision loss affecting his left eye. BSCVA was 20/150, left eye. Fundus examination and baseline SD-OCT imaging obtained on February 9, 2016 revealed a narrow stage-2 full-thickness macular hole associated with clear overlying focal VMT and an elevated retinal flap (2a). On the day of presentation, he decided to undergo PVL instead of a pars plana vitrectomy or ocriplasmin injection. One week after PVL, VMT release was achieved. After 4 days of partial face-down positioning, there was also closure of the macular hole (2b). At 6 weeks later, there was complete closure of the macular hole and BSCVA was improved to 20/30, left eye (2c).

SUMMARY

PVL is a viable alternative to observation, ocriplasmin, and vitrectomy for managing select eyes with symptomatic vitreomacular traction and small stage-2 macular hole. Its robust success rate (particularly with long-acting gases) and high safety profile in comparison to ocriplasmin and its low cost and limited invasiveness in comparison to vitrectomy, make it a highly attractive procedure on a worldwide basis, particularly for treating patients with certain demographic and OCT features affected by focal VMT. To gain level-one evidence to elucidate its potential utility, risks, and limitations, a prospective randomized trial with appropriate controls is indicated.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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