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CLINICAL STUDY

Pneumatic release of focal vitreomacular traction

MG Claus[1], E Feron[2] and M Veckeneer[2]

Abstract

Purpose **To study the efficacy of a single intravitreal injection of expansile gas as a valuable alternative to current treatment options (conservative, pharmacological, and surgical) in patients with symptomatic, focal vitreomacular traction (VMT).**

Patients and methods **This study comprises a retrospective, interventional case series of patients. Twenty eyes in seventeen patients with symptomatic and persisting focal VMT were treated in an outpatient setting with an intravitreal gas injection of 0.2 ml. In 19 eyes, 100% hexafluoroethane (C_2F_6) was used. One eye received sulfur hexafluoride (SF_6). To all but three patients posturing advice was given. Patients were reviewed with a full-eye examination and ocular coherence tomography (OCT) after 14 days and later. The primary outcome measure was the release of VMT on OCT.**

Results **In 17 of the 20 (85.0%) treated eyes, a release of VMT was achieved as documented on OCT. The release of VMT was diagnosed during the first month after injection in 11 eyes of 11 patients and within 3 months in 16 eyes of 15 patients. In all but five of our patients, best corrected visual acuity (BCVA) remained stable or improved. In four patients, the progression or development of cataract was the probable cause of the decrease in BCVA. One patient developed a stage II macular hole after injection and needed vitrectomy. None of the treated patients developed retinal breaks.**

Conclusion **Intravitreal expansile gas injection could offer a minimally invasive, low-cost alternative treatment in patients with symptomatic, persisting VMT. Additional studies on a larger number of patients are required.**

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Introduction

The early stages of an age-related posterior vitreous detachment (PVD) are usually uncomplicated and asymptomatic in most individuals. The initial shallow, localized separation of the vitreous from the perifoveal retina can progress over weeks, months, or even years, until the process is completed at the time of vitreopapillary separation.[1] In some cases, however, persisting vitreomacular adhesion after partial PVD can lead to tractional macular alterations causing symptoms, including decreased visual acuity and metamorphopsia.[2,3] The tractional effects can lead to a number of clinical entities such as the vitreomacular traction (VMT) syndrome, idiopathic lamellar and full-thickness macular hole, maculoschisis, cystoid macular edema, and epiretinal membrane (ERM) formation.[4] Ocular coherence tomography (OCT) has provided a better understanding of the process of PVD and VMT,[1] resulting in a better classification of all stages of VMT.[2,5] Although there are several reports on the natural course of VMT, the frequency of spontaneous release varies widely in the literature.[6,7] Pars plana vitrectomy (PPV) is still the treatment of choice for eyes with broad vitreomacular adhesions and significant ERM component.[2,4] Although the success rate of PPV as a treatment for VMT is high, it carries the risk of cataract formation, endophthalmitis, retinal tear, or detachment.[8–10] Pharmacologic vitreolysis has been investigated extensively in recent years[4,11] as a less invasive approach, particularly in patients with limited vitreomacular adhesion, without significant ERM, with or without a small macular hole. Concerns about toxicity, high market price, and low efficacy in comparison with PPV have limited its broader clinical application.[12–15]

The use of an intravitreal gas injection to induce a PVD was first described in 1995 by Chan and associates in patients with an idiopathic impending or full-thickness macular hole. Other case series using the technique in patients with macular hole, VMT, nonproliferative diabetic retinopathy, and clinically significant diabetic macular edema

[1]Service of Ophthalmology, Ghent University Hospital, Ghent, Belgium

[2]Service of Ophthalmology, ZNA Middelheim, Antwerp, Belgium

Correspondence: MG Claus, Service of Ophthalmology, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium
Tel: +32 9 332 89 16; Fax: +32 9 332 49 63.
E-mail: Margot.Claus@ugent.be

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(DME) without VMT also reported promising results. On the basis of these studies, intravitreal gas injection may offer a minimally invasive, easily accessible, and low-cost alternative treatment for patients with VMT.[2,16–21]In addition, the safety profile of intravitreal gas injection has been well established in pneumatic retinopexy in retinal detachments[22,23] and pneumatic displacement of submacular hemorrhages.[24,25]

We report a case series of 20 eyes in 17 patients that were treated with an intravitreal gas injection to release VMT.

Subjects and methods

This study reports a retrospective case series of patients who elected to undergo an intravitreal gas injection to release VMT between October 2013 and October 2015. The patients were recruited and treated in four general ophthalmic outpatient units. VMT was defined by the OCT criteria put forth by the International Vitreomacular Traction Study Group with evidence of perifoveal vitreous cortex detachment from the retinal surface; macular attachment of the vitreous cortex within a 3-mm radius of the fovea; and association of attachment with distortion of the foveal surface, intraretinal structural changes, elevation of the fovea above the retinal pigment epithelium, or a combination thereof, but no full-thickness interruption of all retinal layers.[5] Focal VMT was graded by three investigators according to the OCT-based classification system as described by Steel *et al*.[26]

Twenty eyes in seventeen patients were treated with an intravitreal gas injection to release VMT. Twelve women and five men, ranging from 58 to 85 years of age, were included. One patient had signs of dry AMD in the treated eye. There were no patients with ERM, exudative AMD, or DME. None of the treated eyes underwent intraocular surgery, retinal laser photocoagulation, or intravitreal injection in the 3 months preceding the intravitreal gas injection. Three eyes were pseudophakic at the time of injection. Demographics, baseline, and post-treatment characteristics are summarized in Table 1.

Pretreatment investigations included Snellen visual acuity, anterior and posterior segment biomicroscopy, tonometry, and OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany; Cirrus, Carl Zeiss Meditec, Dublin, CA, USA; RTVue XR Avanti, Optovue Inc., Fremont, CA, USA; and Opko/OTI Inc., Miami, FL, USA, respectively). The decimal notation of the Snellen fraction is used to report visual acuity. Mydriasis of the treatment eye was accomplished with phenylephrine 10% and tropicamide 0.5%. Povidone iodine 5% was applied around the eye and to the conjunctival sac. Anesthesia consisted of topical drops of oxybuprocaine 0.4%. Using an eyelid speculum, a drape and a 30-gauge needle with a 1-ml syringe, 0.2 ml of 100% hexafluoroethane (C_2F_6) gas (Arceole; Arcad Ophtha, Toulouse, France) was administered intravitreally through the pars plana in

Table 1 Pretreatment and post-treatment characteristics

Case	*Sex*	*Age*	*Eye*	*Lens status*	*HVMA*[a]	*MFT*[b]	*VA pre-injection*[c]	*VA post-injection*[c]	*Release of VMT*[d]	*Time*[e]
1	F	74	LE	Phakic	81	315	0.6	0.9	Y	14
	F	75	RE	Phakic	275	290	0.63	0.63	N	N/A
2	M	73	LE	Pseudophakic	200	280	0.3	0.4	Y	14
3	M	75	RE	Phakic	188	285	0.78	0.7	Y	84
4	F	58	RE	Phakic	41	270	0.8	0.9	Y	35
5	F	60	RE	Phakic	290	390	1.0	1.0	Y	6
6	F	85	RE	Phakic	330	270	0.3	0.4	Y	98
7	F	85	LE	Pseudophakic	400	390	0.5	0.7	Y	91
8[f]	M	59	LE	Phakic	108	345	0.7	0.8	Y	19
9	M	68	LE	Phakic	271	287	0.9	1.0	Y	14
10	M	77	LE	Phakic	211	215	0.7	0.7	Y	14
11	F	71	RE	Phakic	365	343	0.7	0.8	Y	35
12	F	65	RE	Pseudophakic	180	373	1.0	1.0	Y	0[g]
13	F	82	LE	Phakic	289	404	0.8	0.5	Y	15
	F	83	RE	Phakic	454	259	0.5	0.25	N	N/A
14	F	72	RE	Phakic	314	328	0.8	0.63	Y	14
15	F	71	RE	Phakic	358	544	1.0	0.63	Y	14
16	F	75	RE	Phakic	376	519	0.7	0.7	Y	14
	F	75	LE	Phakic	359	388	0.8	0.8	Y	56
17	F	70	LE	Phakic	418	167	0.7	0.3	N	N/A

[a] HVMA, maximal horizontal vitreomacular adhesion (in μm). [b] MFT, maximal foveal thickness (in μm). [c] VA, visual acuity, decimal notation of Snellen fraction. [d] Release of vitreomacular traction yes/no. [e] Time in days from date of injection to first establishment of release of vitreomacular traction and measurement of post-injection VA. N/A, not applicable. [f] Patient treated with sulfur hexafluoride (SF_6) gas; all other patients were treated with hexafluoroethane (C_2F_6) gas. [g] Release of vitreomacular traction was established on the same day as the injection.

19 eyes. One eye received sulfur hexafluoride (SF_6) (Arceole; Arcad Ophtha). Anterior chamber paracentesis was performed in all patients after the gas injection. Most patients were instructed to posture in a prone position from time to time, slowly and repeatedly moving their gaze sideways from one side to the other, as long as they could see the gas bubble. The frequency at which the patients were asked to do this varied from a few times a day to every hour, and this during 5–10 min per session. The rationale of this posturing technique was that by moving the eyes from one side to the other the gas bubble moves inside the eye across the macula and along the vitreomacular insertion, potentially improving the odds of release of the traction. No posturing advice was given in the treatment of three eyes of three patients. The patients were reviewed with a full-eye examination and OCT after 14 days and later.

The primary outcome measure was the release of VMT on OCT. Maximal horizontal diameter of the attached vitreous face at the macula and the maximal foveal thickness between the inner and outer retinal boundaries were noted as measured on OCT image.

Results

A release of VMT was achieved in 17 of 20 (85.0%) treated eyes as documented on OCT (Figure 1). The release of VMT was diagnosed during the first month after the injection in 11 eyes of 11 patients and within 3 months in 16 eyes of 15 patients. In one patient, the release of VMT was established a few hours after the injection.

In one patient who did not respond initially, we decided to perform a second gas injection 2 months after the primary treatment. The initial gas bubble had disappeared after 3 days. Release of VMT was documented 1 month after the second injection. Only the outcome after a single gas injection was considered when analyzing the results for this case series.

A decrease in best corrected visual acuity (BCVA) was seen in four eyes after injection, despite the release of VMT. In these cases, the progression of lens opacification was thought to be the cause of this deterioration. In one eye VMT could not be released and vision decreased from 0.5 to 0.25. One patient developed a stage II macular hole after injection. Her vision was 0.7 before injection and dropped to 0.3 after injection. After vitrectomy she recovered to 0.8.

During follow-up none of the treated patients developed retinal breaks.

Discussion

This study describes the use of intravitreal gas injection for the treatment of VMT syndrome. In this retrospective case series, we found an 85.0% rate of release of VMT. In 10 of 19 (52.6%) eyes of 16 patients treated with C_2F_6 gas VMT was released within 1 month and in 15 (78.9%) eyes within 3 months. In the single patient treated with intravitreal injection of SF_6 gas, VMT release could be demonstrated 19 days after injection. All three pseudophakic eyes included showed VMT release.

The success rate of PPV as a treatment for VMT is high; however, there is a high cost and PPV carries a considerable risk of complications.[8–10] Pharmacologic vitreolysis with ocriplasmin injection can be performed in the office; however, the success rate is lower and, depending on the setting, not more cost-effective than PPV. In addition, recent reports about the current experience with ocriplasmin show that it has possible serious side effects including transient visual loss, lens subluxation, ERG abnormalities, outer retinal changes on OCT, retinal breaks, and dyschromatopsias.[12–15]

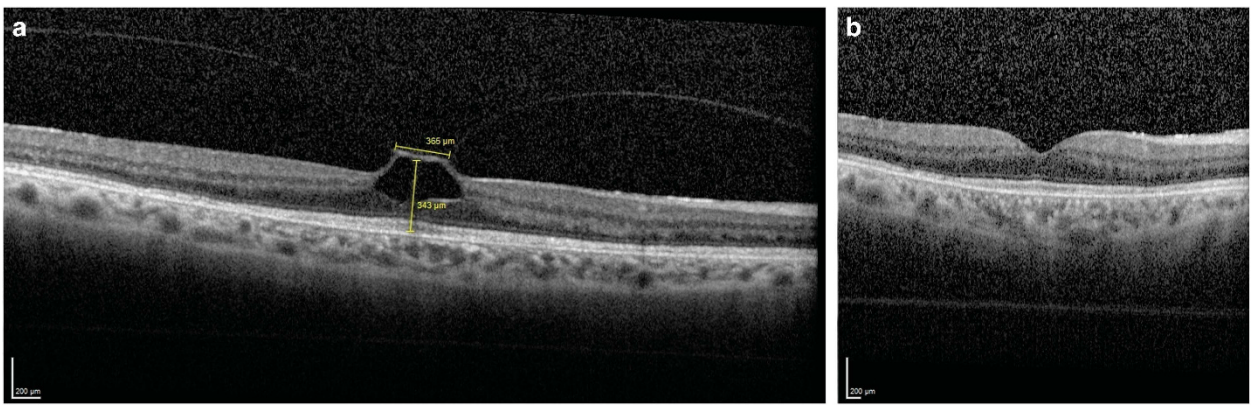

Figure 1 Spectral domain optical coherence tomography of patient with vitreomacular traction before (a) and after (b) injection of hexafluoroethane gas, with the release of vitreomacular traction. The built-in software calipers were used to manually measure the maximal foveal thickness between the inner and outer retinal boundaries and the extent of maximal horizontal vitreomacular adhesion (in this case measuring 343 and 365 µm, respectively).

Pneumatic induction of PVD was first described in 1995 by Chan *et al*,[16] who treated 19 eyes with an idiopathic impending or full-thickness macular hole in 18 patients. Two to nine weeks after injection, a complete PVD developed in 18 of 19 eyes. Jorge *et al*[17] reported a series of six eyes in six patients with an idiopathic stage II macular hole treated by gas-assisted PVD. All patients developed a complete vitreofoveal separation, and the macular hole was closed in five cases. In a case series of Mori *et al*,[18] 19 of 20 eyes with a stage II macular hole achieved a complete PVD after a single intravitreal SF_6 injection. The macular hole was closed in 10 patients. In a case series published by Rodrigues and associates 15 eyes in 14 patients were injected with perfluoropropane (C_3F_8) gas for the treatment of VMT. The authors reported a promising release rate of 40% 1 month after injection.[2] Day *et al*[19] recently reported a case series of nine eyes in nine patients who were treated with intravitreally injected SF_6 for VMT. Five of nine patients (55.6%) had release of VMT 1 month after injection. The use of gas-induced PVD has been described in 12 eyes with nonproliferative diabetic retinopathy and in five eyes with clinically significant DME, without VMT. All treated eyes developed a PVD.[20,21]

Efficacy of pneumatic VMT release, as reported in studies so far, seems higher than that of ocriplasmin.[2,4,11,19] The observed weak and nonsignificant effect of ocriplasmin on pseudophakic eyes (13.4% in the ocriplasmin group *vs* 3.8% in the placebo group)[11] makes the traction release in all three of our pseudophakic cases all the more interesting.

Our results with C_2F_6 injection are slightly more promising compared with previous studies with C_3F_8 and SF_6 injection for the treatment of VMT.[2,19] As SF_6 and C_3F_8 have a, respectively, lower and higher rate of expansion and associated half-life, it is possible that the type of gas used when treating VMT has only minor influence on the result.

It remains unclear whether posturing (with sideways gaze movements) contributed to the resolution of the VMT in some of our cases. All three cases that were not given posturing advice showed release within 3 months. The volume of gas injection on the other hand may be critical in some cases. In fact, in one patient without resolution of the VMT, the gas bubble had already disappeared after 3 days. In normal circumstances, the gas bubble remains present in the eye for at least 14 days, indicating leakage of the gas through the injection site in this case. After repeating the gas injection after 2 months, with the gas bubble remaining in the eye for 16 days, the VMT was released.

The induction of a PVD, whether surgically, pharmacologically, or pneumatically, can increase the risk of retinal break formation as compared with natural history. In our series, none of the treated eyes developed retinal breaks. In previous studies using SF_6 and C_3F_8 injection in patients with VMT, one retinal break was reported.[2,19] In all but four of our patients BCVA remained stable or improved after treatment. A progression or development of cataract was probably the cause of the decrease in BCVA in four patients.

One patient developed a stage II macular hole after injection and needed vitrectomy. Pre-injection OCT showed an interruption of the ellipsoid layer, but no full-thickness macular hole. This disruption in the photoreceptor layer might indicate a risk of developing a full-thickness macular hole. The progression of VMT to macular hole has also been documented both in placebo and ocriplasmin-treated eyes in two phase III studies:[27] 9.6% of placebo *vs* 6.7% of ocriplasmin-injected patients. In a post-marketing survey of adverse events following ocriplasmin, a progression of VMT to macular hole was reported in 92 of 1056 eyes (8.71%).[28]

The best timing for gas injection still remains to be defined. The wide range of percentages of spontaneous release of VMT described in the literature may be explained by differences in patients included. For instance, tertiary referral centers are more likely to include patients with longstanding VMT with less tendency toward spontaneous release. In fact, the lack of large population-based screening studies of different phases of VMT makes it difficult in any particular case of VMT to estimate the relative chances of spontaneous release *vs* evolution toward pathologic conditions such as ERM, lamellar, or full-thickness macular holes. However, there seems to be a general consensus that the spontaneous evolution of a symptomatic VMT should be monitored for a few months before considering possible treatment options, unless the fellow eye has shown a rapid progression toward a full-thickness macular hole.

Whether the gas injections do only accelerate the natural course toward complete resolution or toward pathology such as macular hole formation, as in one patient in the study, is also debatable. On the other hand, longstanding VMT is known to be associated with ERM formation, and therefore it seems reasonable to attempt to avoid this complication by injection of either gas or a pharmacological agent such as ocriplasmin, if VMT does not resolve spontaneously within a few months.

Limitations of this study include the small number of patients, the absence of a control group, and retrospective data collection.

The easy availability, low costs, and the relative safety of gas injections offer a valuable alternative to current treatment options (conservative, pharmacological, and surgical) as a first step approach to nonspontaneously resolving symptomatic VMT. Additional studies on a larger

number of patients are certainly required to further define the best candidates and best timing for gas injection.

Summary

What was known before

- Pars plana vitrectomy has a high success rate as a treatment for vitreomacular traction, but carries risks of cataract formation, endophthalmitis, retinal tear, or detachment.
- Pharmacologic vitreolysis has been investigated extensively as a less invasive approach for focal vitreomacular traction. However, concerns about toxicity, high market price, and low efficacy in comparison with vitrectomy have limited its broader clinical application.
- Pneumatic release of vitreomacular traction has previously been described in two case series with promising results. Intravitreal gas injection to induce a posterior vitreous detachment has also been described in patients with macular hole, nonproliferative diabetic retinopathy, and clinically significant macular edema without vitreomacular traction.

What this study adds

- This article reports the largest case series, so far, of patients treated with intravitreal gas injection to release vitreomacular traction.
- In all but one patient hexafluoroethane gas was used. There are no reports in literature using this gas to treat patients with vitreomacular traction.
- The study demonstrates that this intervention can be very successful in a general outpatient ophthalmic setting as we report the highest release rate of vitreomacular traction treated with a single intravitreal gas injection.

Conflict of interest

The authors declare no conflict of interest.

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