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## Surgical Results in Ocriplasmin Candidates With Symptomatic Vitreomacular Traction Syndrome

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### ABSTRACT

**Purpose:** To report surgical outcomes in a series of cases with symptomatic vitreomacular traction that met MIVI-TRUST (Microplasmin for intravitreal injection-traction release without surgical treatment) criteria for ocriplasmin use who underwent primary 25-gauge vitrectomy.

**Materials and Methods:** A single-center retrospective chart review study was performed in patients who underwent primary 25-gauge vitrectomy for symptomatic vitreomacular traction (VTM) from January 2013 through January 2016. Pre- and postoperative visual acuity (measured by the early treatment diabetic retinopathy acuity test), and posterior hyaloid focal attachment to the macula (demonstrated by high-definition optical coherence tomography) were analyzed. In addition, intra- and postoperative complications were obtained from medical records.

**Results:** Fifteen consecutive cases of symptomatic VMT traction that underwent primary 25-gauge vitrectomy were included. All met the MIVI-TRUST criteria for ocriplasmin use. In all cases, VMT resolution, macular hole closure, and improvement in best corrected visual acuity (BCVA) were observed. Mean visual acuity improved from  $56.53 \pm 16.04$  letters at baseline to  $73.13 \pm 7.46$  letters at 24 weeks of follow-up. The mean BCVA improvement from baseline was 16.60 letters (range 6–44), which was statistically significant ( $P < 0.0001$ ). Ten of fifteen patients (66.6%) showed significant improvement of their BCVA to 20/40 or better (70 or more in ETDRS visual acuity test). No significant intra- or postoperative complications were documented.

**Conclusions:** Primary 25-gauge pars plana vitrectomy in eyes with symptomatic vitreomacular traction is able to efficiently resolve VMT and macular holes, improving vision in candidates for intravitreal injection of ocriplasmin. This well-tolerated surgical procedure may be a reliable and predictable alternative for resolving VMT pathology.

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### KEYWORDS

Retina; vitreomacular traction; ocriplasmin; metamorphopsia; macular hole

## Introduction

Vitreomacular traction syndrome (VMT) is caused by an incomplete posterior vitreous detachment (PVD) and anteroposterior tractional forces leading to anatomic changes in the foveal area with characteristic symptoms and is confirmed by OCT (optical coherence tomography) findings.<sup>1</sup> Treatment of VMT by means of 20-gauge pars plana vitrectomy (PPV) was first described in the 1990s<sup>2–4</sup>, but was with limited success. Although visual acuity improved in most patients, a high rate of complications was reported, including progression of nuclear sclerosis (83%), epiretinal membrane formation (40%), and retinal breaks (20%).<sup>2</sup> Later, a nonsurgical treatment with ocriplasmin (JETREA<sup>®</sup>) was developed, which acts by enzymatically disrupting the pathological attachment between the posterior vitreous cortex and the internal limiting membrane (ILM) of the fovea.<sup>5–7</sup> Recent large trials from the MIVI-TRUST (Microplasmin for intravitreal injection-traction release without surgical treatment) Study Group<sup>8,9</sup> showed relatively low rates of VMT resolution overall (26% vs. 10% of control). However, subgroup analysis demonstrated better outcomes within a subset of

patients. Thus, the MIVI-TRUST report recommends the use of ocriplasmin in patients meeting the following specific criteria: a) presence of native lens, b) absence of epiretinal membrane (ERM), and c) macular hole (MH) less than 400  $\mu\text{m}$  in diameter. In this specific subgroup of patients, VMT management with ocriplasmin may be both low risk and cost-effective compared with other treatment modalities.<sup>8</sup> Here we analyze surgical outcomes in a retrospective series of 15 consecutive patients that meet MIVI-TRUST criteria for ocriplasmin injection and who underwent primary 25-gauge microincision PPV. Postoperative outcomes are reported including change in best-corrected visual acuity, resolution of VMT, closure of MH as well as postoperative complications, including retinal detachment, peripheral retinal breaks, ERM, endophthalmitis, hemorrhage, pain, and cataract development.

## Materials and methods

A retrospective chart review was performed on consecutive patients between February 2013 and January 2016, who underwent primary 25-gauge pars plana vitrectomy

for symptomatic VMT syndrome and met MIVI-TRUST ocriplasmin criteria. The Hospital's Research and Ethics Committee gave its approval for this review. Symptomatic VMT was defined as the presence of metamorphopsia and/or decrease in visual acuity and posterior hyaloid focal attachment to the macula up to 1500  $\mu\text{m}$  demonstrated by HD-OCT five-line raster OCT scan mode (Cirrus HD OCT, Carl Zeiss, Dublin, CA, USA). Patients with macular hole smaller than 400  $\mu\text{m}$  were included if VMT traction was confirmed by HD-OCT. Patients with ERM, prior anti VEGF treatment, or any concomitant retinal disease, such as diabetic retinopathy, macular degeneration, pathologic myopia, or retinal vein occlusion were excluded. All patients provided informed consent for the surgical procedure. A three-port 25-gauge central vitrectomy with Constellation® Ultravit® System (ALCON, Fort Worth, Tx, USA) was performed under local anesthesia with retrobulbar block and sedation. Surgical parameters were set at 5,000 cuts per minute and 650-mmHg vacuum for central vitrectomy. Posterior vitreous cortex separation was addressed with prior application of preservative-free triamcinolone (ATLC, Grin Labs, Mexico, DF, Mexico), which allows for precise visualization of vitreomacular adhesions. Simple aspiration was performed using a vitreous cutter with up to 650 mmHg of suction. Two surgeons utilizing the same technique performed all procedures (AS and JCA). All patients were followed for up to 6 months with early treatment diabetic retinopathy acuity test (ETDRS visual acuity), high-definition OCT (HD-OCT), intraocular pressure, and comprehensive ophthalmic examination recorded. Postoperative complications, such as retinal detachment, peripheral retinal breaks, ERM, endophthalmitis, hemorrhage, pain, and infection were documented. HD-OCT images were obtained with Spectral Domain OCT Cirrus (Carl Zeiss, Dublin, CA, USA) and evaluated for this analysis. Prism GraphPad® 6 (GraphPad Software, Inc., La Jolla, CA, USA) was used for statistical analysis. The Wilcoxon t-test was used for contrast medians of BCVA obtained

before and after surgical intervention. A *P* value <0.05 was considered statistically significant.

## Results

Fifteen VMT cases that met the MIVI-TRUST criteria proposed for ocriplasmin<sup>10</sup> were identified. These patients presented this symptomatology 3 to 6 months prior to their first appointment. All of them were of Hispanic ethnicity with no ophthalmic comorbidities. Female gender was predominant with a male:female ratio of 5:10. There were no patients with bilateral involvement. Patients were on average  $65.93 \pm 7.77$  years of age (range 54–77). The baseline ocular conditions were heterogeneous. The VMT average area evidenced by HD-OCT was of  $488 \pm 301.68 \mu\text{m}$ . Four patients had MH less than 400  $\mu\text{m}$  in diameter. Overall preoperative visual acuity ranged from 20 to 73 letters in ETDRS test (respectively, 20/800 to 20/69 in Snellen notation). All patients were phakic. The demographic and preoperative conditions are shown in Table 1.

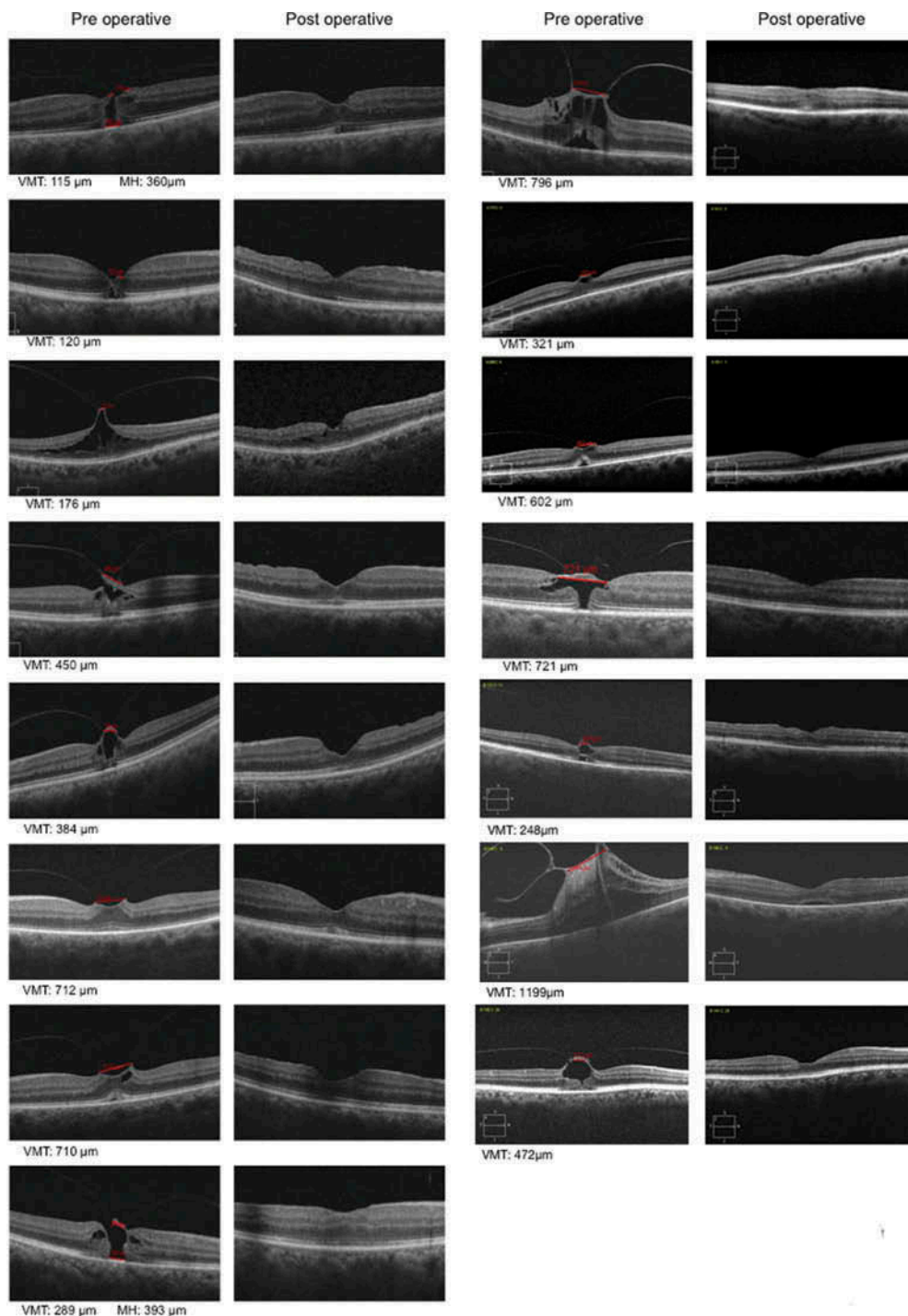
After surgery, macular hole was closed in all cases and patients experienced complete resolution of the VMT, as shown in HD-OCT analysis (Figure 1). Mean visual acuity improved from  $56.53 \pm 16.04$  letters at baseline to  $73.13 \pm 7.46$  letters at 24 weeks of follow-up. Ten patients (66.6%) shown significant improvement of their BCVA to 20/40 or better (70 or more in ETDRS visual acuity test). On average, the group improved  $16.60 \pm 11.36$  letters (range 6–44 letters) in the postoperative period that was clinically and statistically significant ( $P < 0.0001$ ) (Figure 2). On the other hand, maximum BCVA was achieved  $6.67 \pm 3.33$  weeks after surgery (range 3–12) and conserved it until 24 weeks of the clinical follow-up (postoperative results are shown in Table 1). Concerning complications, neither endophthalmitis, retinal detachments, peripheral retinal breaks nor epiretinal membranes were observed during the follow-up period. No hemorrhage, pain, infection, or cataract progression were observed during and following the procedure.

**Table 1.** Baseline clinical characteristics and postoperative results of the study group.

Patient	Gender	Age	Eye	Baseline				Postoperative results					
				Lens status	VMT area ( $\mu\text{m}$ )	Macular Hole	ETDRS visual acuity test	ETDRS visual acuity test	gained letters	Weeks to reach	VMT area ( $\mu\text{m}$ )	cular Hole Clos	BCVA complication**
1	F	65	OS	Phakic	115	Yes	52	70	18	4*	0	Yes	No
2	F	57	OD	Phakic	124	No	58	77	19	12*	0	N/A	No
3	F	77	OD	Phakic	176	No	20	64	44	7	0	N/A	No
4	F	57	OD	Phakic	450	Yes	61	85	24	12*	0	Yes	No
5	F	58	OS	Phakic	384	No	58	69	11	8	0	N/A	No
6	M	76	OD	Phakic	713	No	58	77	19	12*	0	N/A	No
7	M	76	OD	Phakic	710	No	70	78	8	5*	0	N/A	No
8	F	61	OD	Phakic	289	Yes	55	65	10	8	0	Yes	No
9	M	63	OD	Phakic	796	No	61	77	16	4*	0	N/A	No
10	F	75	OS	Phakic	321	No	70	77	7	5*	0	N/A	No
11	M	68	OS	Phakic	602	No	73	79	6	4*	0	N/A	No
12	F	54	OD	Phakic	721	No	63	77	14	3*	0	N/A	No
13	F	63	OD	Phakic	248	Yes	59	65	6	3	0	Yes	No
14	F	70	OS	Phakic	1199	No	20	58	38	4	0	N/A	No
15	M	69	OD	Phakic	472	No	70	79	9	9*	0	N/A	No

BCVA; best corrected visual acuity, ETDRS; early treatment diabetic retinopathy study, OD; right eye, OS; left eye, VMT; vitreomacular traction. \* = BCVA 20/40 or better (Snellen).

\*\* = Including retinal detachment, peripheral retinal breaks, epiretinal membrane, endophthalmitis, hemorrhage, pain, and cataract development.

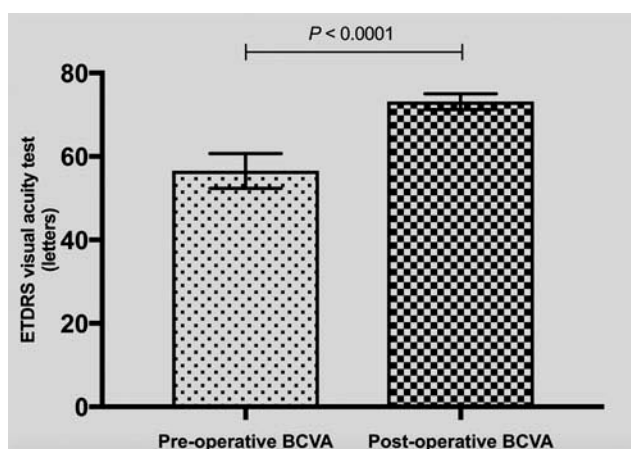


**Figure 1.** HD-OCT images before and after primary 25-gauge vitrectomy in 15 patients with symptomatic VMT syndrome. Cases are exposed consecutively. The VMT average area evidenced by HD-OCT was of  $488 \pm 301.68 \mu\text{m}$ . Patients 1, 4, 8, and 13 had MH less than  $400 \mu\text{m}$  in diameter. After surgery, the macular hole was closed in all cases and patients experienced complete resolution of the VMT, as shown in postoperative HD-OCT images.

## Discussion

The presence of persistent vitreomacular adhesions exerting tractional forces (vitreomacular traction, VMT) cause visual disturbances, including metamorphopsia, blurred vision, and decreased visual acuity, which may negatively affect the patient's health-related quality of life. It may also be associated with the development of macular holes. Ocriplasmin (JETREA®) is a truncated form of plasmin, a human serine protease, and has proteolytic activity against some proteins including laminin and

fibronectin. Plasmin binds to lysine substrate residues through its Kringle domains. It obtained FDA clearance and was released in October 2012. Subgroup analyses from two randomized trials evaluating the efficacy of a single intravitreal injection of  $125 \mu\text{g}$  in symptomatic VMT patients included in two phase 3 clinical trials (TG-MV-006 and TG-MV-007), showed a statistically significant difference in favor of ocriplasmin over placebo for achieving total resolution of VMT at day 28, 26.5% versus 10.1% success rate, respectively.<sup>10</sup> As suggested, this relatively modest rate of success may be higher in phakic eyes without



**Figure 2. Comparison between BCVA before and after primary 25-gauge vitrectomy in 15 patients with symptomatic VMT syndrome.** The preoperative ETDRS visual acuity improve significantly after the surgical procedure (from  $56.53 \pm 16.04$  to  $73.13 \pm 7.46$  letters). On average, the group improved  $16.60 \pm 11.36$  letters that was clinically and statistically significant ( $P < 0.0001$ ). Bars and plots represent the mean  $\pm$  standard error of the mean. BCVA; best corrected visual acuity, ETDRS; early treatment diabetic retinopathy study, VMT; vitreomacular traction.

ERM, with VMT diameter  $< 1500 \mu\text{m}$ , with full thickness macular holes and in patients who are younger than 65 years old. Here we present a series of cases that meet these criteria but instead were managed with primary 25-gauge PPV. In our experience with this case series we obtained a 100% success rate in resolution of VMT, MH closure and improvement of visual acuity. In addition, maximum BCVA was observed on average  $6.67 \pm 3.33$  weeks after surgery, without any significant complication. The development and evolution of surgical devices and equipment for PPV, along with refined surgical techniques have enhanced postoperative outcomes, with low rates of intraoperative complications.<sup>11</sup> This has been similarly observed with phaco-refractive procedures, which achieve predictable, permanent, and definitive improvements in visual acuity. In the same fashion, primary PPV may be considered as a first line treatment for VMT patients in order to preserve vision and avoid progression of vitreous traction in the fovea, with or without associated ERM. In addition, it may represent a valid first line outpatient procedure for VMT patients, since, as this case series suggests, its benefits outweigh its risks.

The surgical technique used in the cases included in this study is a critical factor for obtaining good visual outcomes, since inaccurate macular surgery may create a lamellar or full thickness hole, or may damage foveolar tissue due to surgically induced traction. After a core vitrectomy was performed, the posterior vitreous cortex was identified with the use of triamcinolone, using a preservative-free preparation with micronized particles of  $8\text{--}10 \mu\text{m}$  diameter. After all vitreoretinal attachment areas, other than the center of the macula were identified and released, the foveal area was isolated using a vitreous cutter. Once the adherence between the posterior hyaloid and the optic nerve was released, a small amount of perfluorocarbon fluid was injected in order to stabilize the retina before proceeding with the foveal traction release. A diamond-dusted silicone tip was used in those cases associated with a macular hole after the internal limiting membrane had been removed.

Recent reports have raised safety, cost, and efficacy concerns about ocriplasmin (JETREA®). Abraham et al. reported a case with progressive nyctalopia and visual field defects that correlated with decreased amplitudes in the electroretinogram and decreased reflectivity in the ellipsoid layer that persisted for 2 months after a single injection of ocriplasmin.<sup>12</sup> It may also increase the risk for intraoperative complications in cataract surgery. Keller and Haynes, for example, reported 2 cases that developed zonular dehiscence at the time of vitrectomy and intraocular lens (IOL) implantation after treatment with ocriplasmin.<sup>13</sup> An interesting update of the newly characterized acute ocriplasmin retinopathy has been recently published by Johnson et al.<sup>14</sup>, in which several unexpected signs and symptoms were described, including acute visual acuity decreases, hand motion and light perception, photopsias, dyschromatopsia, nyctalopia, visual field constriction, and disruption of the ellipsoid layer in OCT, among others. These are presumably consequences of the low specificity of this drug, since ocriplasmin is a nonspecific serine protease that cleaves peptide bonds located after a lysine or an arginine residue and, thus is capable of cleaving other proteins.<sup>15</sup> Although vitreomacular adhesion resolution is the primary objective of therapy, visual acuity improvement should also be considered as an important outcome, since they do not always correlate. In a retrospective study of eight VMT patients receiving a single injection of Jetrea®, five eyes experienced complete release of VMT, but only one showed vision improvement.<sup>16</sup> This suggests that ocriplasmin alone may not be sufficient to restore macular function. In addition, considerable side effects and worsening of existing conditions may occur, as reported by Lommatzsch et al. (2014) who observed macular hole enlargement in two patients and massive macular cystoid edema in one patient, after a single injection of ocriplasmin in a cohort of 20 VMT patients.<sup>17</sup> In contrast, a recently published randomized trial, comparing 146 ocriplasmin treated eyes with 74 sham control eyes, showed a higher rate of anatomical success (41.7% versus 6.2%), however, visual improvement of 2 or more lines was only 10% higher in the treated group compared to sham group.<sup>18</sup> If a nonsurgical approach is to be considered, pneumatic vitreolysis has shown better results than ocriplasmin injection, as suggested by Yu et al.<sup>19</sup> On the other hand, microincision vitrectomy has also been shown to be cost-effective, in comparison with intraocular ocriplasmin injection. These findings were published by Chang and Smiddy in an interesting multiple scenario research study that included real costs and Medicare coverage.<sup>20</sup> Although a recent systematic review showed that PPV was associated with higher risks of infection, hemorrhage, and retinal detachment<sup>21</sup>, these complications are likely uncommon, and were not observed at all in our series. Cataract development or progression, however, is a well-known consequence of PPV, with incidence rates as high as 34.7% in a recent systematic review by Jackson et al.<sup>21</sup> VMT syndrome arises from vitreous syneresis, which is strongly associated with aging, similar to cataracts. Given the current advances in cataract surgery, with excellent visual correction and quick outpatient recovery, cataract management has become an accessible and safe procedure. Furthermore, phaco-refractive surgery, even in the absence of cataract has become an increasingly popular and safe alternative for refractive and presbyopia correction. Although cataract progression is a well-known

complication of PPV, this was not observed in our series. This discrepancy may be attributed to the short follow-up period of 24 weeks, with a maximum of 12 weeks to achieve stable BCVA, since the procedure led to prompt visual acuity recovery in the cohort. In conclusion, we are fully aware of the limitations of this report, that only represents our experience in treating VMT (with or without MH) patients meeting ocriplasmin intravitreal injection use criteria, treated with primary PPV. However, we believe it represents a valid, effective, and secure option of treatment. In our opinion, ocriplasmin injection should be reserved as an alternative for patients for whom surgery is formally contraindicated. It is more probable that primary micro incisional pars plana vitrectomy may more reliably and predictably achieve VMT resolution, improve visual acuity, and abolish metamorphopsia than ocriplasmin injection, but prospective additional studies are required to prove this.

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## Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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