Original article

Treatment of vitreomacular traction syndrome with autologous plasmin enzyme

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A R T I C L E   I N F O

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A B S T R A C T

Purpose: To determine whether intravitreal injection of autologous plasmin enzyme (APE) is effective in vitreomacular traction syndrome (VMTS) by improving visual acuity and restoring macular morphology.

Methods: A prospective study of 11 consecutive patients diagnosed with VMTS in the Ophthalmology Department from January to May 2011. Inclusion criteria: best corrected visual acuity (BCVA) less than 0.5, and vitreomacular attachment in foveal area resulting in macular thickness >250 µm diagnosed by optical coherence tomography (Cirrus OCT, Carl Zeiss Meditec, Inc, Oberkochen, Germany). Exclusion criteria: active proliferative diabetic retinopathy, axial myopia >26 mm, vitrectomy, glaucoma, previous intravitreal injections and previous rhegmatogenous detachment. One to the 3 monthly intravitreal injections of 0.2 ml of APE was applied, interrupting if posterior vitreous detachment was attained. Wilcoxon’s test was used for statistical analysis.

Results: A total of 12 eyes of 11 patients were treated. A complete posterior vitreous detachment was achieved in 4 (33%) eyes at the end of the study, 2 of them with one injection, and 2 with 3 monthly injections. Improvement of BCVA was statistically significant (p = 0.017) and the decrease in central macular thickness also was statistically significant (p = 0.016). There was only one complication: intraocular hypertension after injection that subsided with a new paracentesis.

Conclusions: Intravitreal APE injections avoided vitrectomy in VMTS in one in every 3 patients.

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Tratamiento del síndrome de tracción vitreomacular con plasmina autógena

RESUMEN

Objetivo: Analizar si la inyección intravitrea de plasmina autógena es eficaz en el sindrome de tracción vitreo-macular (STVM), mejorando la agudeza visual y restaurando la morfología macular.

Métodos: Estudio prospectivo de 11 pacientes consecutivos diagnosticados de STVM en nuestro Servicio de Oftalmología de enero a mayo de 2011. Criterios de inclusión: mejor agudeza visual corregida (MAVC) inferior a 0,5 y adhesión vitreo-macular foveal, ocasionando aumento del grosor macular central (GMC) > 250 μm diagnosticado mediante tomografía de coherencia óptica (Cirrus OCT, Carl Zeiss Meditec, Inc, Oberkochen, Alemania). Criterios de exclusión: retinopatía diabética proliferante activa, miopia axial > 6 mm, vitrectomía previa, glaucoma, intravitreas previas y antecedentes de desprendimiento de retina. Se realizaron hasta 3 inyecciones mensuales de 0,2 ml de plasmina autógena, evaluándose a las 3 semanas de cada inyección el despegamiento de la adhesión vitreo-macular (AVM), MAVC, GMC y la recuperación de morfología macular en la OCT, interrumpiendo el tratamiento en caso de éxito. Análisis estadístico con test de Wilcoxon.

Resultados: De 12 ojos de 11 pacientes se consiguió despegamiento de AVM en 4 (33%), 2 con una inyección y 2 con 3 inyecciones. La mejoría de la MAVC (p = 0,017) y la disminución del GMC (p = 0,016) fueron estadísticamente significativas, mejorando la morfología macular en todos los casos con despegamiento de la AVM. La única complicación fue un caso de hipertensión intraocular tras la inyección, que cedió repitiendo la paracentesis.

Conclusions: La inyección de plasmina autógena evitó la vitrectomía del STVM en uno de cada 3 pacientes.

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Introduction

The vitreomacular traction syndrome (VMTS) is a disease caused by the partial detachment of the posterior hyaloids with persistence of macular adhesion. This vitreal-macular adhesion (VMA) could cause macular edema and macular cysts. The stage at which the external retina is involved by the traction is regarded as the initial stage of macular holes. It has been demonstrated that the release of VMA improves diabetic retinopathy edema. At present, VMA release can only be achieved by vitrectomy with manual dissection of the posterior hyaloids. However, due to vitreous surgery risks, a few years ago surgeons began to try out intravitreal injection of substances to induce posterior hyaloids detachment, which produced promising results with plasmin and microplasmin.

Plasmin is a proteolytic enzyme obtained from plasminogen activation, utilizing a complex chromatography method or optionally in fresh human plasma by adding streptokinase or urokinase. Microplasmin is a recombinant synthetic product with properties similar to human plasmin but considerably more stable. However, its preparation requires an experienced hematology team to carry out the complex process. Microplasmin has been used to facilitate mechanical vitrectomy in hyaloid traction of diabetic retinopathy and in VMTS. The efficacy of plasmin lies in its proteolytic effect which is free of retinal toxicity as it acts specifically on laminine and fibronectin present in the adhesion area, absolutely respecting the internal limiting membrane due to its lack of activity on collagen type IV.

A multicenter trial, presently in phase 2, is in course to assess treatment with microplasmin as initial therapy for VMTS. The trial comprises 3 syndrome modes: idiopathic VMA, macular hole with traction and diabetic retinopathy tractional macular edema. In addition, the use of autogenic plasmin continues to be researched and the first results indicate that, if activated immediately prior to injection in the surgery, its results could be very similar to those of microplasmin with the advantage that its preparation is easier and less expensive.

The present paper describes the initial results of treatment with autogenic plasmin in a group of patients with VMTS which is very similar to the group of the microplasmin multicenter trial. The main objective of this study is to determine whether autogenic plasmin is able to release VMA. The secondary objectives comprise the assessment of visual acuity evolution and macular thickness in these patients.

Subjects, material and methods

A prospective intervention study in all consecutive patients diagnosed with VMTS in our Ophthalmology Department in its idiopathic, macular hole and tractional diabetes macular edema variants. The study was approved by the Ethical Research Committee of our hospital, which verified
Table 1 – Summary of the main pathological characteristics before and after autogenic plasmin treatment.

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>VA pre</th>
<th>CMT pre</th>
<th>VA post</th>
<th>CMT post</th>
<th>PVD</th>
<th># of inj</th>
<th>Compl.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMTS</td>
<td>0.05</td>
<td>336</td>
<td>0.1</td>
<td>254</td>
<td>No</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>Mac. H.</td>
<td>0.1</td>
<td>243</td>
<td>0.1</td>
<td>220</td>
<td>No</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>trDME</td>
<td>0.2</td>
<td>454</td>
<td>0.5</td>
<td>277</td>
<td>Yes</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>VMTS</td>
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<td>416</td>
<td>0.3</td>
<td>420</td>
<td>No</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>VMTS</td>
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<td>240</td>
<td>0.8</td>
<td>245</td>
<td>Yes</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>trDME</td>
<td>0.2</td>
<td>302</td>
<td>0.5</td>
<td>306</td>
<td>No</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>VMTS</td>
<td>0.2</td>
<td>259</td>
<td>0.2</td>
<td>218</td>
<td>No</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>VMTS</td>
<td>0.3</td>
<td>298</td>
<td>0.3</td>
<td>279</td>
<td>Yes</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>trDME</td>
<td>0.3</td>
<td>453</td>
<td>0.1</td>
<td>266</td>
<td>Yes</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>trDME</td>
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<td>440</td>
<td>0.8</td>
<td>430</td>
<td>No</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>trDME</td>
<td>0.2</td>
<td>320</td>
<td>0.2</td>
<td>320</td>
<td>No</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
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<td>400</td>
<td>0.6</td>
<td>390</td>
<td>No</td>
<td>1</td>
<td>No</td>
</tr>
</tbody>
</table>

Mac. H.: macular hole; VA post: visual acuity post-treatment; VA pre: visual acuity pretreatment; Compl.: complications; PVD: posterior vitreous detachment; trDME: tractional diabetic macular edema; CMT post: central macular thickness posttreatment; CMT pre: central macular thickness pretreatment; # of inj: number of injections; VMTS: idiopathic vitreomacular traction syndrome.

compliance with the Helsinki standards. The inclusion criteria comprised best corrected visual acuity (BCVA) of 0.5 or less in the best eye and over 0.1 in the worst eye, assessed by a technician who did not participate in the study applying Early Treatment Diabetic Retinopathy Study (ETDRS) optotypes transformed to decimal scale, and foveal VMA, producing increased central macular thickness (CMT) diagnosed by means of optic coherence tomography (Cirrus OCT, Carl Zeiss Meditec, Inc., Oberkochen, Germany). The inclusion period began in January and ended in May 2011. Exclusion criteria comprised active proliferative diabetic retinopathy, axial myopia exceeding 26 mm, previous vitrectomy, poorly controlled glaucoma, intravitreal injections within the 3 preceding months and retina detachment history.

VMA was diagnosed with spectral domain OCT scanning the presence of posterior hyaloids traction in “butterfly wings”

Fig. 1 – OCT before and after the injection of autogenic test mean in case #8, showing posterior vitreous detachment and macular morphology recovery after a single injection.
in contact with the foveolar area, producing surrounding edema, cystic cavity or foveolar fossa deformation. The CMT measured in microns in the area of maximum traction was recorded. In the baseline examination and subsequent check-ups, a complete ophthalmological examination was carried out including BCVA, tonometry, quantification of corneal and lens opacities, fundoscopy and retinography.

After obtaining informed consents, the patients were injected with 0.2 ml of intravitreal plasmin prepared from 9 cc of each patients’ blood extracted 1 h earlier and prepared in the surgery by a hematologist expert, centrifuging and treating it with urokinase (Urokinase Vedim®, 100,000 UI, Vendim Pharma, Sant Cugat Del Valles, Spain) according to the technique described by Rizzo and improved by Díaz-Llopis.16 The injection technique was similar to that applied for intravitreal injections of antiangiogenics with the difference that the eyes required previous paracentesis. After the treatment, broad range antibiotic eye drops were prescribed for 6 days.

The patients were reviewed at week 3, assessing the hyaloids detachment and recovery of macular morphology as well as changes in CMT by means of OCT and BCVA with ETDRS optotypes. For the cases which did not exhibit VMA release, a new injection was proposed at one month after the first one, repeating the procedure up to a maximum of 3 injections, after which the patients who had not obtained detachment were referred for vitrectomy. In addition, the possible complications related to the procedure were registered. The results were analyzed by the Wilcoxon test and percentage comparisons.

Results

Twelve eyes of 11 patients were treated (4 males and 7 females) with a mean age of 74, with one having both eyes treated. The main pathological characteristics of the eyes before and after the study are summarized in Table 1. At the end of the study, 5 eyes had received one injection and 7 had received 3 injections. Four eyes (33.3%) achieved the detachment at the end of the study, 2 with a single injection (Fig. 1) and 2 with 3 injections. CMT improvement after the injections was statistically significant ($p = 0.016$) (Fig. 2). Seven eyes (58.3%) experienced statistically significant BCVA improvements of one line or more ($p = 0.017$) (Fig. 3). Only one severe complication arose, a sudden increase of intraocular pressure immediately after the injection which was resolved with a new paracentesis. No complications occurred in the ocular surface with the exception of subconjunctival hemorrhages typical of intravitreal injections.

Discussion

The use of substances to facilitate posterior vitreous detachment (PVD) during vitrectomy has given rise to the possibility

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**Fig. 2** – Graph showing central macular thickness changes in patients with and without posterior vitreous detachment after autogenic plasmin injection. The mean went down from 328 to 278 μm after treatment.

**Fig. 3** – Graph showing visual acuity improvement in eyes with PVD after intravitreal injection of autogenic plasmin. The mean increase from 0.2 to 0.35 after treatment.
of using intravitreal injections as an isolated treatment for VMTS. The MIVIT trial is a multicenter study which established the most adequate dose of intravitreal microplasmin for obtaining PVD \(^{11}\) in the first phase, while in the second phase it is utilizing intravitreal injections as baseline treatment for VMTS. Recently, it has published VMA detachment results in 44% of eyes with a single injection and in 58% with 3 injections. The autogenic plasmin utilized in the present study has obtained slightly lower (one in every 3 patients) but also significant percentages considering that it allowed patients to avoid vitrectomy. Instead of the complex preparation process required by microplasmin, the autogenic plasmin of the present study was obtained with simple plasminogen hydrolyzed with urokinase. In contrast with other authors, this study did not use streptokinase as it exhibits vitreous turbidity and frequent post-surgery inflammation,\(^{10}\) even at the risk of plasmin doses being slightly lower. Despite this shortcoming, the authors were able to achieve significant visual acuity improvements and diminished GCMM after the injection, even in some eyes which did not exhibit complete VMA detachment. These symptomatic improvements could be due to the relaxation of the hyaloid traction caused by the proteolytic effect of plasmin,\(^{12}\) as the OCT of said patients revealed perimacular partial detachments which perhaps could have been better documented with high resolution echography. In addition, the improvements exhibited by the cases which did not exhibit VMA detachment could be due to other effects of plasmin on macular edema (not yet studied in depth) as could be deduced from the positive effects of intravitreal plasmin in diffuse diabetic macular edema\(^{13}\) and in retinal venous branch thrombosis\(^{14}\) which cannot be explained by tractional factors. The authors wish to point out a minor bias which could be caused by the mechanical action of the intravitreal injection with paracentesis due to its ocular decompression effect which could play a small role in VMA release.

In conclusion, the present study indicates that plasmin obtained from autogenic plasma appears to be a reasonable alternative to microplasmin as a baseline treatment for VMTS due to the fact that it is easier and less expensive to obtain. However, studies with considerably higher amounts of patients are necessary in order to definitively establish its role as a therapeutic agent in VMA.

**Conflict of interest**

No conflict of interests has been declared by the authors.

**References**