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Role of Single Dose of Intravitreal Recombinant Tissue Plasminogen Activator in Vitreomacular Traction and Associated Macular Edema: a Retrospective Study

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ABSTRACT

Introduction: *To evaluate the role of single dose of intravitreal recombinant tissue plasminogen activator (RTPA) in patients with vitreomacular traction (VMT) and macular edema.*

Methodology: *Eighteen eyes of 18 patients with VMT and macular edema, as evidenced by spectral domain optical coherence tomography (SD-OCT), were selected in our Malda Medical College. After proper history taking and required systemic examinations, each patient underwent detailed ophthalmic examination, including best corrected visual acuity (BCVA), intraocular pressure, slit lamp examination, fundal evaluation by indirect ophthalmoscopy, 78D, 90D lens. All patients underwent SD-OCT examination to evaluate central macular thickness (CMT). Then, after proper informed consent, intravitreal injections with 50 micrograms of RTPA were administered to each patient and all baseline examinations were repeated one month and three months after injection.*

Results: *Postoperatively, 16 patients had complete posterior vitreous detachment (PVD) and 14 resolution of VMT. All participants showed an improvement in BCVA and reduction in CMT.*

Conclusion: *Intravitreal RTPA might be a useful agent in resolution of VMT associated with macular edema.*

Keywords: recombinant tissue plasminogen activator, vitreomacular traction, macular edema, posterior vitreous detachment.

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ABBREVIATIONS

RTPA=recombinant tissue plasminogen activator
VMT=vitreomacular traction
SD-OCT=spectral domain optical coherence tomography
BCVA=best corrected visual acuity
CMT=central macular thickness
PVD=posterior vitreous detachment
PVR=proliferative vitreoretinopathy
PPV=pars plana vitrectomy
ILM=internal limiting membrane
IOP=intraocular pressure

INTRODUCTION

Collagen fibrils of vitreous cortex are adhered to internal limiting membrane of the retina at the site of macula by laminin and fibronectin (1-4). With age, vitreous gets liquified along with loosening of vitreoretinal adhesions (5-7). If vitreous is incompletely separated from the macula, it will result in vitreo macular adhesion, which may be the cause of VMT syndrome at a later stage.

In 1967, Jaffe was the first to describe the VMT, which is caused by the separation of vitreous from peripheral retina, while the central macular area remains attached to the vitreous (8). Whenever vitreous constriction occurs, it will generate vitreous traction both antero-posteriorly and tangentially (9). Traction over fovea may cause macular edema, which is ultimately leading to macular hole.

Proliferative vitreoretinopathy (PVR) and incomplete PVD can lead to VMT syndrome, which is characterized by reduction in visual acuity, metamorphopsia, occasional double vision. Vitreomacular traction is suspected when leakage at the optic disc or macular edema is found.

Vitreomacular adhesion might have an impact in the progression of diabetic retinopathy, age related macular degeneration and central retinal vein occlusion (10-13); as a result, PVD induction can be tried with success in dealing with the macular edema associated with the three above-mentioned disorders (14, 15).

To deal with VMT with PVR, pars plana vitrectomy (PPV) is the preferred option. Enzymatic vitreolysis is often employed to ease PVD induction. The principle of enzymatic vitreolysis is to liquefy the vitreous cortex as well as to lyse adhesion between the internal limiting membrane (ILM) and vitreous.

Recombinant tissue plasminogen activator is a specific serine protease which transforms plasminogen into plasmin and it is primarily used in subretinal hemorrhage (16, 17), but can also be fruitfully used in induction of PVD and thus might be a possible key to the resolution of VMT as well as associated macular edema (19-21).

The main aim of our study was to see the role of a single dose of intravitreal RTPA (50 micrograms) in VMT with macular edema. ❑

METHODOLOGY

This hospital based non-randomized retrospective interventional study was conducted in Malda Medical College, India, over a period of 14 months (January 2019 to February 2020). It was approved by the institutional ethics committee and it followed the tenets of the Declaration of Helsinki.

Eighteen eyes of 18 patients of both sexes were included in our study based on the following inclusion criteria: age over 18 years, informed consent from the patient, confirmation of diagnosis by detailed fundal evaluation along with ultrasonography-B and SD-OCT scans. Patients with already existing PVD, proliferative diabetic retinopathy, media opacity (corneal edema/cataract), uncontrolled glaucoma, high myopia, severe peripheral retinal degeneration, active uveitis, hypersensitivity to active substances, pregnancy/lactation or history of prior vitrectomy were excluded from the study.

Outcome measures included achievement of complete PVD, resolution of VMT, improvement of BCVA, and reduction in CMT.

At first, a detailed history about the onset of dimness of vision, its progress, any distortion of image along with history of systemic illness if any was taken. Then, a systemic examination was performed with special attention to blood pressure. From the ophthalmological examination point of view, each patient underwent BCVA measurement by Snellen's chart, intraocular pressure (IOP) measurement by Goldmann's applanation tonometry, detailed slit lamp examination as well as detailed fundal evaluation with

the help of indirect ophthalmoscopy, 78D and 90D lens. Then, each patient underwent SD-OCT examination to evaluate CMT.

Patients who were using antithrombotic agents were advised to stop that medication one week prior to procedure.

After that, every patient was advised to go for complete blood count, blood sugar estimation, blood pressure measurement, ECG and needed physician clearance for undergoing the procedure. Recombinant tissue plasminogen activator should be preserved in -70 degree centigrade after proper reconstitution.

After the prior informed consent for the off-label use of this drug, RTPA (50 micrograms/0.05 mL) was injected to every patient intravitreally 3.5-4 mm away from limbus in the supero-temporal quadrant, under topical anaesthesia with proparacaine, after properly disinfecting the concerned eye with povidone-iodine.

Best corrected visual acuity, IOP measurement, detailed slit lamp and fundal evaluation along with SD-OCT to measure the CMT were repeated one month and three months after the intravitreal injection.

Normal CMT in SD-OCT is taken as 225±25 microns. A reduction of 50 microns in CMT is regarded as clinically significant. One line improvement in Snellen's chart was also considered clinically significant.

All data were analysed by using SPSS software and put for paired t-test.

RESULTS

Among the 18 participants to our study (15 males and three females) aged 40-60 years, 16 patients showed complete PVD and 14 had resolution in VMT. All patients improved in terms of BCVA and reduction in CMT (Figures 1 and 2).

Here, BCVA was converted into LogMar chart and then data were obtained after applying paired t-test using SPSS software.

Tables 1, 2, 3 and 4 clearly show that there is a definite improvement in terms of BCVA correction along with reduction in CMT. P values were <0.003 one month after intervention in relation to BCVA improvement, and became 0.001 three months post-intervention. However, p value in relation to CMT always remained <0.001 from one month after intervention onwards up to three months. ❑

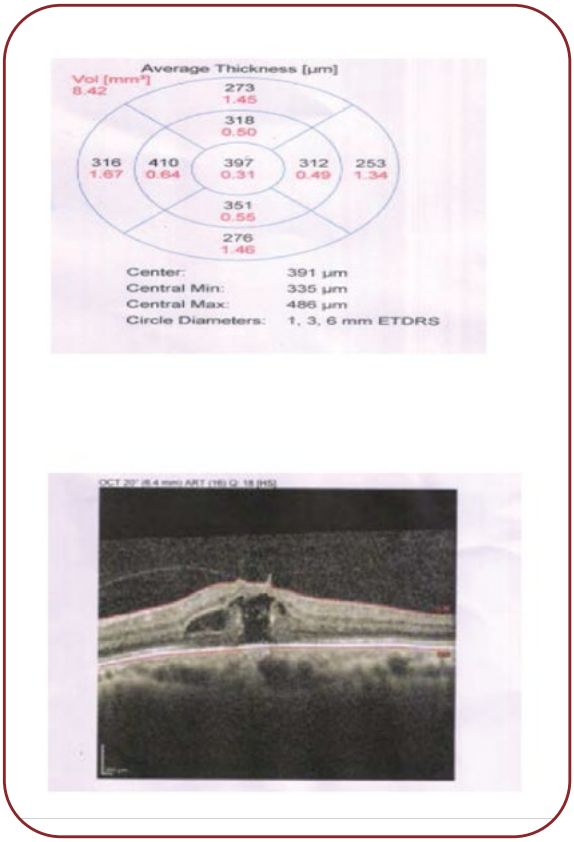

FIGURE 1. Spectral domain optical coherence tomography image obtained at baseline

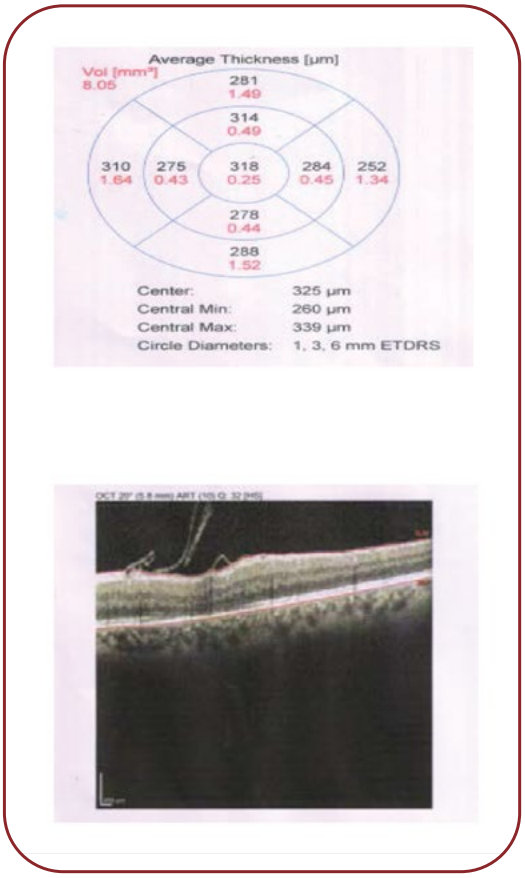

FIGURE 2. Spectral domain optical coherence tomography image obtained three months post-intervention

TABLE 1. Mean, standard deviation, correlation coefficient in relation to best corrected visual acuity

	Baseline	One month post-intervention	Three months post-intervention
Mean	0.833	0.65	0.5722
Standard deviation	0.1534	0.1855	0.1526
Correlation coefficient		0.6	0.796

TABLE 2. Mean, standard deviation, correlation of coefficient in relation to central macular thickness

	Baseline	One month post-intervention	Three months post-intervention
Mean	485.4444	435.6667	426.4444
Standard deviation	36.7491	39.1663	36.0216
Correlation coefficient		0.997	0.989

TABLE 3. T-test value and P value by paired t-test in relation to best corrected visual acuity

	Baseline	One month post-intervention	Three months post-intervention
T-test value		3.2314	5.1192
P value		<0.003	<0.001

TABLE 4. T-test value and P value by paired t-test in relation to central macular thickness

	Baseline	One month post-intervention	Three months post-intervention
T-test value		3.9322	4.8644
P value		<0.001	<0.001

DISCUSSION

In young patients, PVD induction by mechanical means is a very difficult task, given the tight adherence of vitreous with retina, and iatrogenic retinal holes might be found in such cases (22, 23). Nowadays, PPV is often clubbed with ILM peeling because ILM is believed to provide scaffolding for the proliferating astrocytes, which is the culprit for proliferating retinopathy.

Enzymatic vitreolysis has often been employed to tackle this kind of disorders. Pharmacologic agents such as plasmin, hyaluronidase, collagenase and chondroitinase were tried with varying success; however, most of them are no longer in use due to inadequate clinical efficacy, complications, or both (24). Ocriplasmin, a truncated form of plasmin, can be a useful agent in doing vitreolysis, as proved by different studies conducted on both animal and human subjects (25).

Recombinant TPA, an inert and sterile agent, has got different clinical uses (19). Vitreoretinal interface is mainly composed of laminin and fibronectin, which can be lysed by plasmin, which in turn is activated by TPA, and thus, cleavage is induced between the posterior vitreous cortex and the retina (21). In human eye, the safe dose range for intravitreal injection of TPA has been reported to be between 25 and 100 micrograms (26). It does not have any toxic effects on retina and at the same time, it does not produce cataract.

In our study, we have found an improvement in BCVA as well as reduction in CMT one month after intravitreal RTPA, which were still present three months post-intervention. The coefficient of correlation in relation to BCVA improvement jumped from 0.6 one month after intervention to 0.796 three months post-intervention, whereas that coefficient remained almost unchanged in relation to CMT (0.997 and 0.989) – thus, the reduction in CMT was associated with BCVA improvement, which remained satisfactory even three months post-intervention. T-test value in relation to BCVA moved in a positive direction from 3.2314 to 5.1192 (from one month to three months post-intervention), accompanied by the same positively directed movement of t-test value in relation to CMT from 3.9322 to 4.8644, respectively. Again, our findings revealed a strong difference in BCVA and CMT between the two the groups, which actually reflected the positive impact of the intervention on disease outcome. According to Hikichi *et al*, when vitreous is separated from the macula, spontaneous resolution of macular edema occurs (27). Actually, in eyes with VMT, vitreous contains very little amount of plasminogen compared to retinal vascular diseases, where plasminogen is ample due to blood retinal barrier breakdown. For this reason, RTPA acts better in the context of retinal vascular diseases. But it is to be remembered that enzymatic vitreolysis is not the alternative of PPV along with ILM peeling – rather it can facilitate the PPV to be done.

Large tractional band associated with ERM is very difficult to be managed by enzymatic vitreolysis and it should be dealt with surgical intervention. Moreover, thick bands with tissue element on the top of fibrin with prolonged duration are more often refractory to medical management.

The main drawback of the current study was that it had a non-randomised design and included a small number of patients who were followed-up for a short period of time. So, a prospective randomised study with a larger sample size, a longer duration and multiple doses of injection is required to draw firm conclusion. ❑

CONCLUSION

Intravitreal injection of 50 micrograms of RTPA can be a reliable weapon for the induction of complete PVD in patients who have VMT without coexisting epiretinal membrane. It can also improve BCVA and decrease CMT, thus yielding patients' satisfaction. Hence, it might be employed as a useful adjunctive measure for subsequent PPV with ILM peeling. ❑

Conflicts of interest: none declared.
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