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ORIGINAL RESEARCH

Effectiveness of Mp-3 Microperimetric Biofeedback Fixation Training For Low Vision Rehabilitation in Patients Treated With Corticosteroid Ivt in Retinal Vein Occlusions

Mariaelena Malvasi[1], Sabrina Compagno[1], Alessandro Segnalini[1], Vito Maurizio Malvasi[2], Fernanda Pacella[3], Paolo Turchetti[4], Elena Pacella[1]

[1]Department of Sense Organs, Faculty of Medicine and Dentistry, Sapienza University of Rome, Rome, Italy; [2]Department of Odontostomatological and Maxillo-Facial Sciences, Sapienza University of Rome, Rome, Italy; [3]Department of Ophthalmology, Carlo Poma Hospital, Mantua, Italy; [4]National Institute for Health, Migration and Poverty (INMP/NIHMP), Rome, Italy

Correspondence: Elena Pacella, Department of Sense Organs, University Sapienza, Rome, Policlinico Umberto I, Viale, del Policlinico 155, Rome, 00161, Italy, Email elena.pacella@uniroma1.it

Background: The success of fixation training using microperimetric biofeedback (MP-3 MBFT) in the realm of visual rehabilitation for patients with central vision loss caused by macular pathologies is well established. This study aimed to assess the effectiveness and safety of visual rehabilitation with microperimetric biofeedback in consolidating the benefits obtained, with the goal of reducing the need for repeated intravitreal injections (IVT). Specifically, the focus is on the eyes of patients with central vision loss treated with slow-release corticosteroid IVT following retinal venous thrombosis (RVO), aiming to enhance and maintain postoperative efficacy.

Methods: This retrospective review involved the examination of 44 eyes affected by macular edema due to RVO associated with central vision loss. Patients were divided into two groups, with only one undergoing ten sessions of 10-minute visual rehabilitation with a microperimeter (MP-3 MBFT) after IVT over a period of 20 weeks.

Results: All the treated patients demonstrated good tolerance to the procedure, with no reported complications. A comparison of best-corrected visual acuity (BCVA), retinal sensitivity recorded with a microperimeter, and pre-IVT fixation stability revealed statistically significant improvements at the end of the first month after IVT. However, the treatment group continued to exhibit superior and more enduring results at four months post-IV.

Conclusion: The synergistic use of MP-3 MBFT rehabilitation after IVT with slow-release corticosteroids has proven particularly effective in improving BCVA and long-term fixation stability. This led to a significant reduction in the number of required IVTs, with no related adverse events. The authors argue that biofeedback utilization represents a noninvasive therapeutic option devoid of contraindications and easy to implement and that it positively contributes to the overall patient experience regarding quality of life in advanced stages of macular diseases.

Keywords: microperimetric biofeedback, visual rehabilitation, macular edema, intravitreal corticosteroid, retinal vein occlusion

Introduction

Retinal vein occlusions (RVOs) are among the leading causes of visual disabilities and represent a vascular problem that affects more than 16 million people worldwide,[1–3] especially those aged 70 and and hypertension are strong risk factors for RVO.[1,2,4] Others risk factors include: dyslipidemia, diabetes mellitus, vasculitis, factor V Leiden mutation, antic-ardiolipin antibodies, low levels of vitamin B12. Smoking is another important risk factor.[5–10]

Some ocular conditions such as glaucoma or ocular hypertension have been shown to increase the risk for CRVO.[5,11–13] RVOs can involve the central retinal vein (CRVO), or one of the peripheral venous branches (BRVO).[12]

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Macular edema (ME) is the main cause of loss of visual acuity (VA) in RVO, and the chronic form of edema causes irreversible damage to retinal photoreceptors.[5]

Currently, there is no well-defined therapeutic treatment for RVO. Intravitreal injections (IVT) of anti-VEGF agents and corticosteroids are commonly used in clinical practice to manage ME and stabilize the blood–retinal barrier.[14] However, their effectiveness in regressing ME progression has limitations, including the need for repeated injections with potential complications.[2,4,5]

Nowadays few studies in literature had investigated the effectiveness of rehabilitation via biofeedback training via the MP1 device in RVO patients treated with intravitreal corticosteroids, this involves monitoring and improving retinal functions through biological feedback provided by the MP1 device.[5]

Visual rehabilitation, particularly microperimetric biofeedback training (MBFT), is known to enhance fixation stability and overall visual performance.[15,16]

The Microperimetric Biofeedback Training (MBFT) is a visual rehabilitation strategy aimed at improving fixation stability by creating a new preferred fixation point. This approach involves retraining the visual system to adapt to a new visual condition, promoting communication between the retina and the brain and subsequent cortical plasticity.

MBFT establishes a new preferred fixation point, and through its use, it is possible to assess retinal sensitivity and fixation stability in a combined manner, allowing for diagnosis and visual rehabilitation even in patients with fixation problems.[17]

The biofeedback method involves instructing patients to choose a final fixation position, thereby improving visual reading speed and using a new peripheral retinal area to perform visual tasks. This area, called the Preferred Retinal Locus (PRL), acts as a new oculomotor reference point.[17]

Oculomotor training would result in an increase in gray and white matter density in the cerebellum, indicating learning in performing visual tasks with eccentric vision.[18]

Microperimetric biofeedback contributes to strengthening the PRL and enhances activation of the visual cortex.[19,20] In particular, auditory feedback increases attention modulation,[21] contributing to identifying the final PRL and improving fixation stability.[15]

Ideal PRLs maintain stable visual images, track moving targets, and allow for rapid shifts in fixation. Biofeedback training aims to strengthen an existing PRL or select a new favorable fixation target.[22]

The microperimeter allows for the precise identification and mapping of PRLs on the retina, while retinal sensitivity helps choose an appropriate area for fixation reinforcement and smooth reading.[22]

The retinal position adopted for fixation corresponds to the foveal center, which is why fixation stability is usually compromised in people with central vision loss.[22]

The mechanism by which MBFTs improve visual function is not entirely clear, but a new retinal locus with new fixation points is believed to be established.[23–26] The study suggested that oculomotor exercise combined with MBFT and IVT may contribute to functional recovery by stimulating photoreceptors involved in the edematous process.[19,27,28] This may also enhance pump mechanisms in retinal cells responsible for expelling/reabsorbing toxic substances, potentially reducing the need for frequent IVT injections.[23–25]

This study explored the potential of combining slow-release corticosteroids IVT[14,19] with visual rehabilitation through the use of MBFTs to decrease the number of injections and improve visual performance in patients with ME due to RVO.[29]

Material and Methods

To explore this synergistic therapeutic approach, a retrospective study was conducted to assess the impact of visual rehabilitation through photostimulation treatments with biofeedback on improving outcomes in RVO patients treated with slow-release corticosteroid IVT.

Patients affected by RVO was investigated at the Ophthalmic Ophthalmology Unit, Policlinico Umberto I, in Rome. The study followed the Declaration of Helsinki and obtained approval from the Sapienza University of Rome's Ethics Board.

The study involved two groups: Group A (24 eyes) underwent combined intravitreal treatment (IVT) with dexamethasone (DEX) and biofeedback, while Group B (24 eyes) received only IVT of DEX.

The patients were further divided into groups based on the type of vein occlusion: central venous occlusion (CRVO group, 8 patients) and branch venous occlusion (BRVO group, 16 patients). The characteristics of the patients examined are shown in Table 1.

Patients in both groups provided written informed consent, including consent for microperimetric biofeedback sessions in Group B. All patients had macular edema from retinal vein occlusion, and eligibility criteria were strictly applied.

In our study, we examined the variation in visual function, with particular attention to the parameter of best-corrected visual acuity (BCVA) at high contrast, successfully used in numerous multicenter clinical studies.[30–33] In fact, in accordance with the United States Food and Drug Administration (FDA), this parameter is the primary endpoint for evaluating the effect of new therapies through changes in visual function in assessing ocular conditions.[34]

We also evaluated fixation stability, revealed by the "cloud" of points indicating the retinal area used for fixation, the Preferred Retinal Locus (PRL). Fixation stability is crucial, especially in individuals with central vision loss, where instability can compromise visibility. Improving fixation stability is one of the main goals of microperimetric training programs, thereby contributing to overall visual function improvement.[35–38]

Another parameter considered in our study is retinal sensitivity, which records the correct response of retinal photoreceptors to the brightest stimulus intensity.[39]

The primary study endpoints included evaluating the efficacy of retinal photoreceptor stimulation/reactivation, assessed in terms of LogMar, ETDRS, Central Macular Thickness, Mean Retinal Sensitivity, Fixation, through microperimetric biofeedback therapy (MBFT) and assessing the clinical course of MBFT in patients receiving intravitreal DEX implantation. The secondary endpoint aimed to determine whether combining MBFTs could enhance the effectiveness of IVT with DEX over time, potentially delaying the need for additional injections.

The study, registered as ClinicalTrials.gov Identifier NCT02257333, adhered to protocol number 1.0 and was approved on July 1, 2014. The average time between RVO diagnosis and treatment initiation was 62.5 days. This research aimed to contribute valuable insights into the potential benefits of combining MBFT therapy with IVT combined with DEX for patients with retinal vein occlusion.

Eligibility Criteria

The eligibility criteria for patients were as follows:

- age ≥ 18 years;
- Patients with macular oedema secondary to central or branch retinal vein occlusion.
- visual acuity < 5/10, < 45 letters on the ETDRS, equivalent to a LogMAR between 1 and 0.2;
- central macular thickness (CMT), assessed by OCT, ≥ 285 µm.

Table 1 Sampling of Patients in the Biofeedback Group and in the Control Group

CHARACTERISTICS OF THE SAMPLE		
	Biofeedback Group	**Control group**
Number of eyes	24	24
Average age and DS	66,83±15,31,	69,83 ±12,41
Sex	M=10; F=14	M=16; F=8
Number of eyes with CRVO	8	8
Number of eyes with BRVO	16	16

Only naïve patients who had not previously received any intravitreal or laser treatment for venous occlusion prior to our study were included.

Exclusion Criteria

The exclusion criteria were as follows:

- BCVA in the better eye equal to or better than 20/60;
- previous laser treatments;
- previous intravitreal injections;
- systemic diseases: uncontrolled arterial hypertension and diabetes;
- evolved cataract;
- glaucoma;
- A positive history of intraocular pressure increase induced by topical steroids;
- the epiretinal membrane was evident on OCT;
- age-related macular degeneration (AMD);
- vitreous surgery performed less than three months prior;
- Patients who had cataract surgery performed less than six months previously;
- Laser yag capsulotomy performed less than two months prior;
- uveitis
- State of pregnancy
- Severe corneal alterations such as keratopathy;
- severe vitreous opacity
- other active eye diseases (such as conjunctivitis, uveitis, scleritis and optic neuritis);
- inability to complete the entire course of biofeedback sessions.

Exclusion Criteria Assessment and Follow-Up

All patients who were candidates for treatment had a thorough general medical history and a preoperative medical examination.

Prior to injection (T0), patients underwent a specialist examination, which included the following steps:

- Assessment of best corrected visual acuity (BCVA), expressed in Etdrs/LogMar (Early Treatment Diabetic Retinopathy Study);
- Objective examination of the anterior segment via biomicroscopy
- ocular tone measurement with Goldman's optical applanation tonometer;
- Observation of the ocular fundus via a binocular indirect ophthalmoscope;
- Performance of optical coherence tomography (OCT) (SD-OCT; Spectralis, Heidelberg, Germany)
- Performance of microperimetry with MP-1 for the study of retinal sensitivity and fixation
- The follow-up examination performed the day after the injection included
- evaluation of the anterior segment under a slit lamp
- ocular tone measurement;
- ophthalmoscopic examination of the ocular fundus.
- Subsequent follow-ups were established at one and four months (T1, T4) after injection and included the following:
- assessment of best corrected visual acuity (BCVA) in the ETDRS and logMAR;
- Slit-lamp anterior segment assessment;
- ocular tone measurement;
- ophthalmoscopic examination of the ocular fundus;
- Performance of optical coherence tomography (OCT) (Spectralis HRA-OCT from Hei-delberg Engineering);
- Performance of microperimetry with MP-1 for the study of retinal sensitivity and fixation.

From T1 to T4, rehabilitation treatment with biofeedback was performed, and the patients were evaluated at months 1 to 4.

The four parameters whose values we analysed at baseline and at the 1st and 4th months (T0, T1, T4) were as follows:

- best corrected visual acuity (BCVA), expressed in ETDRS and logMAR
- central macular thickness (CMT)
- Mean retinal sensitivity (MRS)
- Fixation stability.

Best Corrected Visual Acuity (BCVA)

During the first visit and at subsequent follow-ups, each patient's visual acuity was assessed with Early Treatment Diabetic Retinopathy Study (ETDRS) tables placed at a distance of 5 m.

Optical Coherence Tomography (OCT)

The tomographic images were obtained using the Spectralis HRA-OCT device from Heidelberg Engineering (software version 3.2) with the following protocol: volumetric scanning of 512×49 scans (49 lines, 512 A-scans per line); scanning area: 6×6 mm; acquisition time per scan: 15.0 seconds; and radial scans of 6 mm oriented at 30° intervals and centred on the foveal region.[40–42]

Microperimetry

A Nidek MP-1 microperimeter equipped with the Navis operating system was used for the study. An automatic macula 12°10 dB scheme with a 4–2 threshold strategy and Goldmann III stimulus was chosen for retinal sensitivity determination.

Ten rehabilitation sessions with biofeedback lasting 10 minutes each were performed from month 1 to month 4 after IVT of DEX.

Treatment was applied only to the eye affected by OCVR ME, while in cases where both were affected (n5 paz), the eye with a lower BCVA and greater macular thickness than the other was selected; the latter was taken as the control eye to evaluate the disease course.

In this study, an MP-3 microperimeter (NIDEK Technologies Srl, Padua, Italy) with audio biofeedback signals, known as microperimetric biofeedback training (MBFT), during which an increase in the auditory frequency occurs as the target approaches the desired alignment,[15,43] was used to help patients during the oculomotor exercise training process, which is an essential part of visual rehabilitation as it improves visual saccades and "pursuit movements".

The MP-3 microperimeter enabled real-time monitoring of fixation 30 times per second using a high-sensitivity, high-speed infrared camera to achieve automatic correction of eye movement. The automated MP-3 microperimeter program uses a 4–2 threshold strategy with a Goldmann III model, and the size of the fixation target during training is decided by the trainer, an experienced ophthalmologist. The retinal light threshold was measured using a Goldmann III with stimulus intensities between 0 and 34 dB and a stimulus duration of 200 ms.[44]

In the present study, the standard target was a red cross subtending 1°, but in the treated eye of the patients in our study, it was increased to ≥2°.

An auditory signal present during training became continuous when the fixation was in the optimal position and intermittent when it was far from this point.[15]

During training, the trainer instructed the patient to make eye movements to control the auditory signal with the aim of maintaining a continuous signal. Furthermore, patients were encouraged to use this eye movement control in their daily life. In this study, the rehabilitation programme consisted of three sessions of 10 minutes per eye performed twice a week for 20 consecutive weeks, whereas rehabilitation protocols with MBFT are variable and usually occur weekly over a period of 5 to 10 weeks, with each session lasting approximately 10 minutes.[15,44]

The slow-release IVT of dexamethasone (Ozurdex®) (0.7 mg active ingredient) is a potent corticosteroid that suppresses inflammation by reducing edema, fibrin deposition, capillary permeability, and phagocytic migration in the inflammatory response.

Currently, intravitreal implantation of DEX is the only drug approved by the FDA for the treatment of macular edema secondary to RVO, and this drug has a good safety profile.

After injection, patients were monitored throughout the follow-up at 1 week and 1.4 months.

Statistical Analysis

The analysis was conducted with SPSS Package 19.0 for Windows.

The significance level was set at $p \leq 0.05$ (5%).

The statistical analysis involved the use of frequency tables and the calculation of central tendency (mean and median), dispersion (minimum and maximum) and standard deviation. The trend over time of the variables of interest was graphed using line graphs. To calculate the significance of the data, ANOVA was performed for repeated measures, followed by post hoc Fisher's PLSD test. The differences in time from T0 to T4 for all 5 variables taken into analysis (logMAR, ETDRS, CMT, MRS, and fixation) were statistically significant ($p<0.0001$).

The variables LogMar, ETDRS, CMT, and MRS were influenced by pathology (CRVO and BRVO), with $p<0.0001$.

For the variable fixation, the effects of pathology ($p<0.0001$) and biofeedback treatment ($p<0.01$) were significant.

With regard to the individuals in the examined group who underwent IVT and biofeedback therapy, the patients were further divided into those who underwent central fixation on the microperimetry examination and those who underwent eccentric fixation (Table 2).

Results

At baseline (T0), before injection, the following parameters were assessed in the biofeedback group (Table 3) and in the control group (Table 3):

The patients were evaluated after the 1st and 4th months after the intravitreal implantation, and the values are shown in Tables 3 and 4 for the biofeedback group and the control group, respectively.

By calculating the average differences in the T0→T1 and T0→T4 time intervals for ETDRS, CMT, MRS, and fixation, the following comparative tables were produced between the biofeedback group and the control group, which showed an average increase or decrease in CRVO and BRVO (Table 4). Graphs were then made showing the development over time at T0, T1 and T4 in the Control and Biofeedback groups for each variable: ETDRS (Figure 1), LogMar (Figure 2), CMT (Figure 3), MRS (Figure 4) and Fixation (Figure 5).

Table 2 Outcomes of Patients Undergoing Rehabilitation Therapy with MBFT (Biofeedback Group) Characterized by Central Fixation and Eccentric Fixation and Fixation Stability (%) Calculated Before and After Rehabilitation

Microperimetry	Timing	Medium sensitivity	Medium defect	Fixation	Fixation Stability
Group 1 Central Fixation	Pre IVT	9,8 dB	−8,0 dB	predominantly central, stable	Pre rehabilitation 79%
	1° month post IVT	10,9 dB	−8,0 dB	predominantly central, stable	
	4° month post IVT	13,5 dB	− 4.8 dB	stable	Post rehabilitation 97%
Central Fixation overall					18%
Group 2 Eccentric Fixation	Pre IVT	2,2 dB	−14,3 dB,	predominantly eccentric, relationally unstable	Pre rehabilitation 50%
	1° month post IVT	8,1 dB	−9,1 dB	predominantly eccentric, relationally unstable	
	4° month post IVT	5,2 dB	− 12.3 dB	stable	Post rehabilitation 67%
Eccentric Fixation overall					17%

Table 3 Clinical Evaluation of Patients in the Control Group and Biofeedback Group at T0, T1 and T4 (Mean ± SD) for the Number of Letters (ETDRS), CMT (Central Macular Thickness), MRS (Central Macular Thickness) and Fixation

Parameters evaluated in the Control Group							Parameters evaluated in the Biofeedback Group					
	CRVO			BRVO			CRVO			BRVO		
	T0	T1	T4	T0	T1	T4	T0	T1	T4	T0	T1	T4
Number of Letter ETDRS	0,86 ± 0.09	28 ± 5.23	20,75 ± 5.32	27,5 ± 5.16	38,13 ± 4.79	37,12 ± 5.94	9,5 ± 5.26	28,75 ± 4.87	24,25 ± 4.5	30,38 ± 9.53	38,75 ± 9.29	44,63 ± 9.24
LogMar	11 ± 4.5	0,58 ± 0.1	0,7 ± 0.08	0,54 ± 0.11	0,31 ± 0.1	0,33 ± 0.14	0,93 ± 0.09	0,53 ± 0.1	0,6 ± 0.12	0,49 ± 0.19	0,3 ± 0.15	0,21 ± 0.17
CMT (µm)	568 ± 29.98	246 ± 25.98	273,75 ± 26.69	428,13 ± 75.84	234 ± 40.35	251,38 ± 42.83	587,25 ± 41.03	247 ± 37.56	259,25±41,24	462,88 ± 50.91	265,37 ± 37.18	269,25 ±15,52
MRS (dB)	3,45 ± 0.82	9 ± 2.1	6,52 ± 2.58	6,9 ± 1.28	9,13 ± 1.99	8,74 ± 2.36	3,02 ± 0.69	10,4 ± 2.58	9,18 ±3,53	7 ± 1.98	9,36 ± 1.54	10,56 ± 2.38
Fixation (%)	37 ± 3.74	70,75 ± 4.03	69,83 ± 4.36	77,38 ± 4.31	81,25 ± 2.92	80,63 ± 2.97	38,25 ± 7.27	72,5 ± 5.44	83,25 ± 7.26	78,12 ± 5.03	83,52 ± 4.57	92,13 ± 5.84

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Table 4 Comparison of CRVO and BRVO for the Intervals T0→T1 and T0→T4

	CRVO				BRVO			
	Biofeedback Group		Control Group		Biofeedback Group		Control Group	
	T0→T1	T0→T4	T0→T1	T0→T4	T0→T1	T0→T4	T0→T1	T0→T4
ETDRS	+19	+14	+17	+9	+8	+14	+10	+9
CMT	−340	−328	−322	−295	−197	−193	−204	−187
MRS	+7	+6	+5,6	+3,3	+2,3	+3,5	+2,2	+1,8
Fixation	+34	+46	+33	+32	+5	+14	+4	+3

Discussion

In the last two decades, microperimetry has been widely used to characterize functional vision in a wide range of retinal conditions. Microperimetry has already been adopted as an endpoint in interventional studies to identify early variations in visual function and monitor its changes during various retinal diseases. However, to date, there are no studies in the

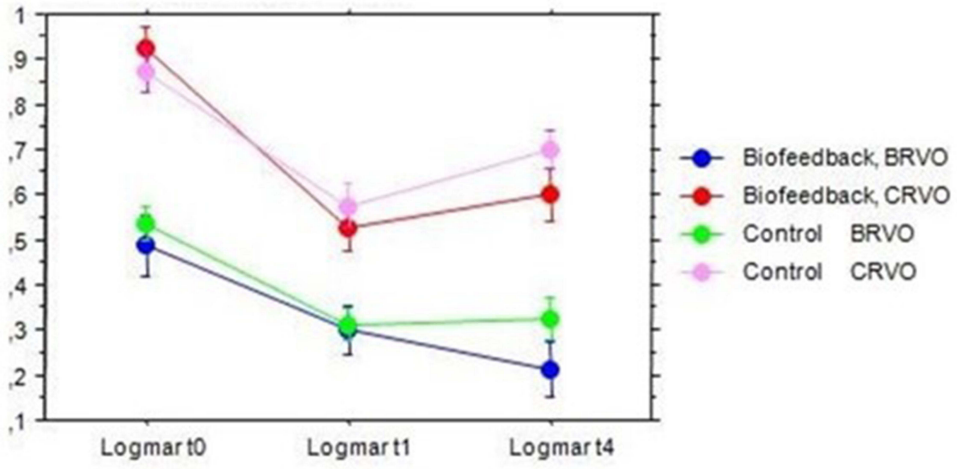

Figure 1 Development of the LogMar variable over time.

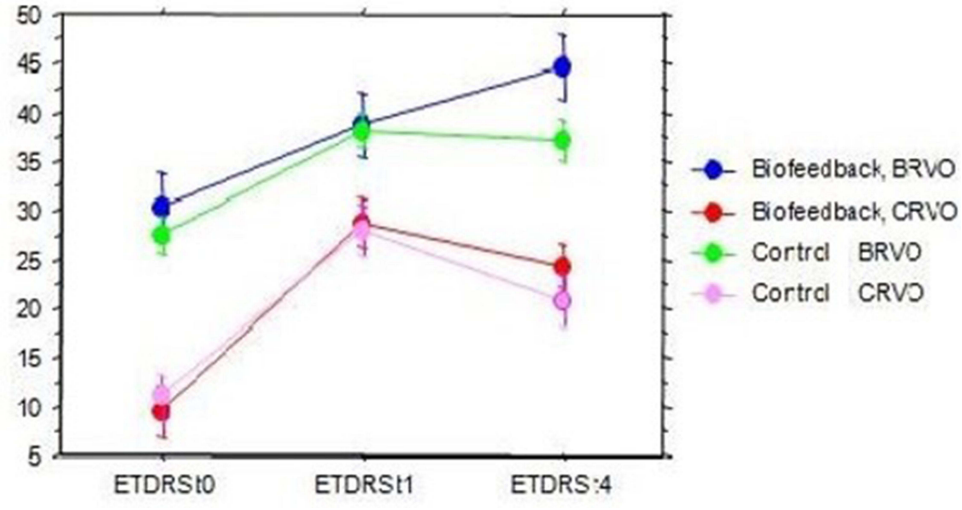

Figure 2 Time course of the ETDRS variable over time.

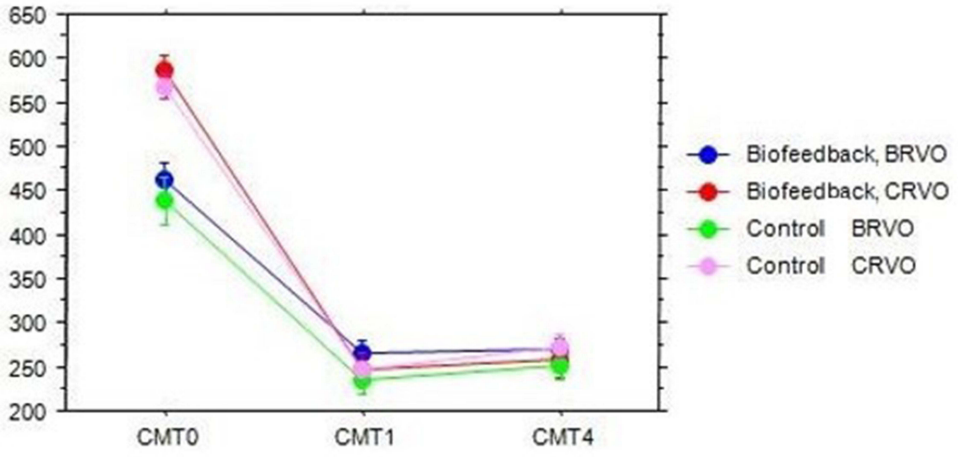

Figure 3 Development of the CMT (Central Macular Thickness) variable over time.

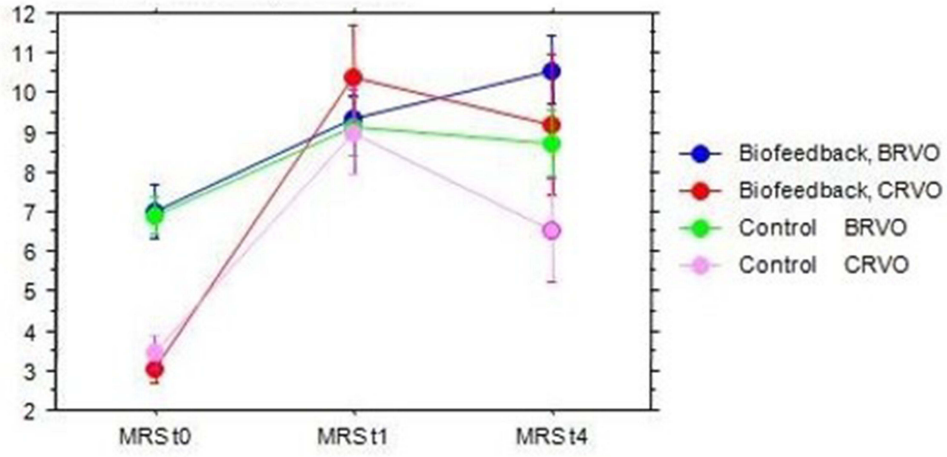

Figure 4 Development of the MRS (mean retinal sensitivity) variable over time.

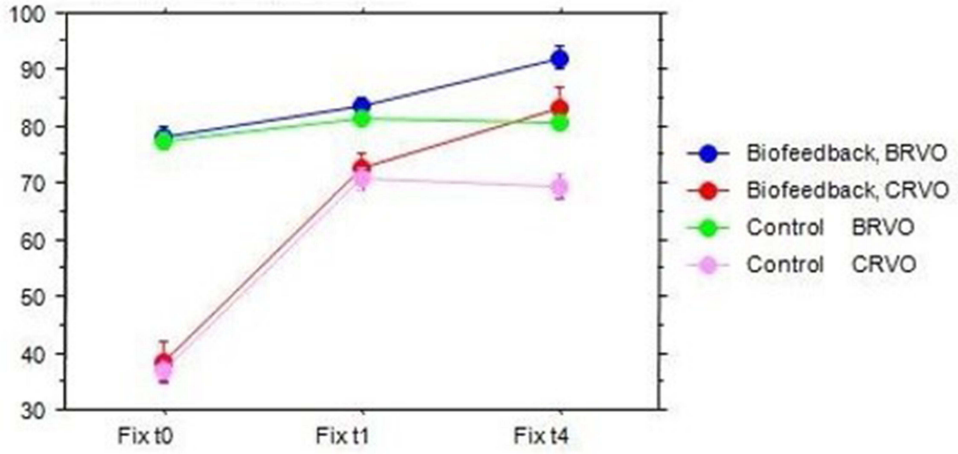

Figure 5 Development of the Fixation variable over time.

literature employing the use of microperimetry in synergy with therapies for retinal diseases, as summarized in the review by Sì Yang et al.[45]

Our study shown the results of rehabilitation therapy using MBFT showed long-term stabilization in terms of fixation (Table 4), with an overall 18% gain in fixation for almost both groups (Table 4).

The effectiveness and safety of the DEX implant have been scientifically validated.[2,14] The main objective was to assess the efficacy of rehabilitative therapy using microperimetry (MBFT) in patients with retinal vein occlusion (RVO) treated with slow-release DEX.[2,14] These results indicate that slow-release DEX is effective at treating macular edema resulting from RVO, confirming the findings of the existing scientific literature. The combination of intravitreal DEX (DEX IVT) and MBFT significantly improved best-corrected visual acuity (BCVA), average retinal sensitivity, fixation, and reduction in central macular thickness compared to monotherapy with slow-release DEX.[46,47]

MBFT microperimetry has proven effective in selecting the best fixation position and improving fixation stability, reading speed, acuity, and quality of life in patients with central vision loss caused by RVO.[29,44]

The combination of DEX IVT and MBFT led to early edema reduction and structural restoration of retinal cells, as well as stimulation of nerve synapses through biofeedback. This contributed to the functional restoration of retinal nerve cells, which are essential for visual recovery in patients with macular disease.

Conclusion

In conclusion, the combination of DEX IVT and MBFT rehabilitation improved visual performance, especially during central fixation, with a tendency toward long-term stabilization after repeated biofeedback treatments.

The need for validated endpoints for retinal diseases has been widely discussed.[36–38] An ideal endpoint should be easily and frequently measurable, repeatable with minimal measurement and assessment errors, sensitive to changes over time and treatment effects. In this regard, the evaluation MFBT's parameters holds clinical relevance and is significant for patients.[48]

In recent years, there has been a significant increase in the use of microperimetry (MP) in research, as diseases affecting the macula can cause unstable and/or eccentric fixation, making MP an interesting tool for their assessment.[49] Moreover, fixation characteristics can change during disease progression, and MP devices can quantify and monitor these changes, synergistically supporting the therapy administered to the patient to achieve a more enduring visual recovery over time.

By reducing the frequency of DEX IVT injections, a positive impact on patient quality of life[50] can be achieved, with consequent economic benefits from the reduced management of chronic conditions. Future studies with larger sample sizes and longer follow-up periods are suggested to optimize the treatment regimen for RVO in combination with IVT therapies.

Disclosure

The authors report no conflicts of interest in this work.

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