Essential Elements of the Protocol and Statistical Analysis Plan

Brief Title:

Study on the recovery of visual perceptual function dysfunction in patients with diabetes

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Catalogue

1. Current Status of Clinical Trials and Research Objectives

1.1 Research Status

1.1.1 Significance of Visual Perceptual Learning Training for Diabetic Retinopathy Patients

Diabetic retinopathy (DR) is one of the most common chronic complications of diabetes and a leading cause of visual impairment in adults[1]. In China, the prevalence of DR among diabetic patients is as high as 23%, with 3 ~ 4 million patients losing their vision annually due to DR[2-3], severely impairing their visual function and quality. Traditional research has focused on diabetic retinal vascular lesions, with vascular endothelial changes being the only clinically successful therapeutic target for DR patients. Current clinical treatments primarily address retinal vascular damage. However, we have observed that even after surgical treatment or retinal laser photocoagulation, DR patients with stable conditions still experience significant visual dysfunction, lacking further treatment options to improve visual function. This highlights the urgent need to explore effective rehabilitation methods for visual dysfunction in DR patients after clinical treatment stabilization.

1.1.2 Domestic and International Progress in Visual Perceptual Learning

Visual perceptual learning (VPL) training refers to a method of improving the visual system's ability to perceive external visual information through repeated specific visual tasks. In 2014, Sabel BA and Gudlin J[4-5] conducted a randomized clinical trial on "vision restoration training" for glaucoma patients, demonstrating significant improvement in visual function in the training group compared to the control group. Sabel BA proposed the "residual vision activation theory," suggesting that in cases of retinal or visual cortex damage (e.g., glaucoma, stroke, amblyopia, age-related macular degeneration), repeated stimulation can enhance electrical conduction and synchronization among partially damaged neural synapses and downstream neural networks, leading to partial recovery of visual function[6]. The visual system can actively adapt to and reflect changes in the external environment. When synaptic strength and quantity change and persist over time, this process is termed neuroplasticity. Its manifestations include induced dendritic growth or shortening, changes

in dendritic density, functional adjustments, and subsequent cortical reorganization and neurovascular regeneration[7]. Studies have also shown that amblyopic patients can improve visual function through occlusion therapy or training, and even adult amblyopia may benefit from repeated perceptual learning[8]. Yan and Zhou J[9] conducted a randomized clinical trial on 23 myopic subjects, training the non-dominant eye at the cutoff frequency. Post-training, subjects showed improved contrast sensitivity and visual acuity at the trained spatial frequency, with effects lasting at least four months. These results suggest that VPL may offer a non-invasive training method to compensate for optical defects in mild to moderate myopia. Aimola L[10] demonstrated that perceptual learning could partially improve visual perception in stroke patients, mitigating visual field defects caused by stroke. Age-related visual decline is common, and VPL can effectively improve near reading ability in individuals with early presbyopia symptoms[11]. These studies indicate that the visual system retains plasticity across age groups, and VPL is the most widely used method to modify visual system plasticity and promote visual function recovery.

1.1.3 Mechanisms of Perceptual Learning Training

Visual perception learning training refers to the method of improving the visual system's ability to perceive external visual information by continuously performing specific visual training tasks [12]. The neural mechanism of visual perception learning has always been a research focus and difficulty in this field, although a lot of exploration has been conducted from the aspects of neurophysics and neurobiology, it is still very unclear. There are mainly four theories: (1) the plasticity theory of the primary cortex [13] : perceptual learning can make the neural encoding of stimuli in the primary cortex more accurate; (2) Reweighting Theory [14]: By readjusting the weights of stimulus information in visual processing, the theory aims to enhance the efficiency of utilizing such information. (3) Reverse Hierarchy Theory: Visual signals are expressed in a top-down manner by feedback from the higher cortex to the primary cortex; (4) Dual plasticity theory [15]: Perceptual learning may trigger the plasticity of the visual cortex towards stimulus attributes and task types. However, in fact, more research has not integrated different models into a unified perspective, and several issues highly

related to the core mechanism of VPL have become increasingly controversial. Scholars have trained macaques on direction recognition tasks [16]. Compared with untrained macaques, the neurons in the V4 region of the trained macaques showed stronger responses and improved direction recognition ability after training. There are also studies using functional magnetic resonance imaging (fMRI) to investigate brain area activation during contrast discrimination task training [17]. In the early stages of training, there is strong activation in the higher visual cortex, while in the later stages, activity in the lower visual cortex increases, indicating that visual perception learning training can activate corresponding brain areas to improve visual function. However, the relationship between the lower and higher visual cortices is complex and requires further research to prove.

The current clinical treatment methods are often difficult to make the visual function of patients with diabetes retinopathy (DR) fully recover to the normal level, and lack of follow-up treatment methods to further improve the visual function. How to find an effective way to restore the visual function of DR patients after damage is an urgent problem to be solved. This study conducted online remote visual perception learning training based on Internet cloud computing for DR patients who were in stable condition after surgery, and comprehensively evaluated the changes of visual perception function of DR patients before and after training by using perceptual function detection combined with OCT and psychological scale. The purpose was to evaluate the improvement effect of visual perception training on DR patients' visual function and influencing factors, and provide guidance strategies for the evaluation, follow-up and rehabilitation treatment of visual function after DR clinical treatment.

1.2 Research Objectives

1.2.1 To explore the improvement of visual perceptual function in DR patients through VPL training.

1.2.2 To provide guidance for visual function recovery in DR patients with visual impairment.

2. Type of Study Design

Prospective, randomized controlled clinical study.

3. Inclusion and Exclusion Criteria for Subjects

3.1 Inclusion Criteria:

（1） Pre-treatment diagnosis of moderate-to-severe non-proliferative or proliferative DR, with the affected eye having undergone pan-retinal photocoagulation at least 4 weeks prior or vitreoretinal surgery at least 8 weeks prior, with stable conditions and no macular edema or recurrent retinal hemorrhage.（2）Best-corrected ETDRS visual acuity (BCVA) ⩾ 0.1.（3）Clear refractive media.（4）Age ⩽ 65 years, able to understand and cooperate with examinations and training.

3.2 Exclusion Criteria:

（1）Significant refractive media opacity or other ocular diseases affecting visual function (e.g., high myopia, glaucoma, strabismus, amblyopia, macular degeneration).（2）History of psychiatric disorders affecting cognitive function, alcoholism, or traumatic brain injury.（3）Postoperative ocular complications within 8 weeks prior to testing.

3.3 Elimination Criteria:

（1）Temporary refusal of examination or withdrawal from the study.（2）Incomplete examination records.

4. Expected Number of Cases Required

Sample Size: 24 cases (estimated using G*Power analysis, increased to 36 to account for potential dropout rates).

5. Experimental Methods

5.1 Grouping

Subjects are randomly assigned to the Visual Perceptual Learning Training (VPLT) group or the Control Group (CG) using random number generation.

5.2 Study Design

Only the surgical eye is included (for bilateral surgery, the eye with better vision meeting inclusion

criteria is selected). The VPLT group undergoes 40 minutes of daily monocular VPL training for 3 months, with follow-ups at 1 and 3 months. The CG receives no training and is followed up after 3 months.

5.3 Assessments:

Non-contact intraocular pressure measurement.

Ultra-widefield laser scanning fundus examination to exclude glaucoma and new hemorrhages.

Refractive correction for BCVA.

Optical coherence tomography (OCT) and OCT angiography (OCTA) for retinal blood flow and structural parameters.

Visual perceptual function assessment using a Matlab R2016a-based program, including:

Grating acuity (GA) at 0.8 contrast.

First-order motion stimulus perception sensitivity (1stM) at 2.0 c/d spatial frequency.

Second-order contrast stimulus perception sensitivity (2ndS) at 1.0 c/d spatial frequency.

Second-order motion stimulus perception sensitivity (2ndM) at 2.0 c/d spatial frequency.

Hospital Anxiety and Depression Scale (HADs) and Low Vision Quality of Life Questionnaire (LVQOL), administered by the same researcher.

6. Clinical Observation, Follow-up, and Measures to Ensure Subject Compliance

Clinical Observation: Indicators as described in the experimental methods.

Follow-up: Conducted via telephone.

Compliance Measures: Detailed contact information is collected during hospitalization, with timely follow-up via phone or WeChat post-surgery.

7. Criteria for Discontinuing Clinical Research and Regulations for Ending Clinical Research

Discontinuation Criteria: Subjects may withdraw at any time. The study must be terminated immediately if safety risks arise.

Ending Criteria: The study concludes when the last subject completes the final follow-up.

8. Data Management and Regulations for Data Traceability

Subject-related documents are archived per Chinese laws, retained for at least 5 years post-study. All subject data, including identifiable information and medical records, are confidential. Participants are informed of data confidentiality procedures before signing consent forms. Research team members must maintain confidentiality unless authorized.

9. Subject Coding, Random Number Table, and Procedures for Storing Case Report Forms

Same as Section 8.

10. Adverse Event Recording, Reporting, and Follow-up

Any serious adverse events are reported immediately to the clinical trial leader, with detailed documentation of timing, handling measures, and outcomes.

11. Statistical Analysis Plan

Statistical analysis was performed based on the per-protocol (PP) principle. Data are presented as mean ± SD for normally distributed continuous variables, median (P_{25}, P_{75}) for non–normally continuous variables, and frequency (percentage) for categorical variables. The Shapiro-Wilk test was employed to assess the normality of the continuous variables. For normally distributed variables, between-group differences were assessed using unpaired t-test. Repeated measures analysis of variance (ANOVA) and simple effects analysis were conducted to examine changes in visual perceptual function and psychological status before and after VPL training. For each participant, the magnitude of improvement for each visual perceptual function (ΔGA, Δ1stM, Δ2ndS, Δ2ndM) was calculated using the formula: $\boldsymbol{\Delta I} = 20\ log10\ (Post\text{-}training\ Measure\ /\ Pre\text{-}training\ Measure)$ dB. Spearman correlation analysis was performed to evaluate the relationships among general demographic characteristics, visual perceptual function, retinal structure and blood flow parameters,

and psychological scale scores. Multivariable linear regression models were then constructed with ΔGA, Δ1stM, Δ2ndS, and Δ2ndM as dependent variables to identify factors associated with training efficacy.

12. Quality Control and Quality Assurance

The principal investigator conducts regular monitoring, including pre-study and interim on-site audits.

13. Subject Recruitment and Informed Consent Process

Before each patient is enrolled in this study, the research physician has the responsibility to provide a complete and comprehensive introduction to the purpose, research process, and potential risks of this study to the patient or their designated representative. Patients should be informed of their rights, risks, and benefits. Prior to enrollment, patients should sign an informed consent form and keep it in electronic medical records.

14. Expected Progress and Completion Date

Clinical trial completion: August 2024.

15. Follow-up and Medical Measures After the Study

None.

16. Responsibilities of All Parties and Other Regulations

None.

17. References

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