RESEARCH PROTOCOL

Title:
Subthreshold micropulse yellow (577 nm) laser versus half-dose photodynamic therapy for central serous chorioretinopathy : a randomized controlled pilot study

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The protocol is compliance with ICH-GCP.

Keywords: Subthreshold micropulse laser, photodynamic therapy, half-dose, central serous chorioretinopathy, randomized study

Background

Central serous chorioretinopathy (CSCR) is characterized by 1 or more serous detachments of the neurosensory retina commonly associated with retinal pigment epithelium (RPE) detachments[1]. There is a broad spectrum of clinical presentations. [2] Visual blurring, micropsia, dyschromatopsia, and metamorphopsia are common symptoms. One or more retinal pigment epithelium (RPE) leakage points and punctuate hyperfluorescent spots can be observed in fluorescein angiography (FA) and indocyanine green angiography (ICGA). [3] CSCR resolves spontaneously within 6 months in more than 80% of patients, reaching a visual acuity of better than 20/30.[4] However, treatment is indicated in patients requiring faster visual recovery or in those with permanent visual impairment secondary to CSCR in the fellow eye or in patients with chronic CSCR. [5]

Photodynamic therapy (PDT) and focal laser are the main stay of treatment for CSCR. [5] Photodynamic therapy (PDT) has been reported to be an effective treatment option for CSCR in most patients.[6-8] The therapeutic mechanism of PDT is postulated to be caused by short-term choriocapillaris hypoperfusion and long-term choroidal vascular remodeling, which reduces choroidal congestion, vascular hyperpermeability, and extravascular leakage.[9, 10] However, potential side-effects of PDT, including RPE atrophy, neuroretinal thickness (NRT) thinning, development of choroidal neovascularization (CNV), and reduction in macular function have been reported.[9, 11-13] Some studies have reported the treatment of CSC with modified PDT parameters, including reduced dose ($3mg/m^2$) of verteporfin or reduced fluence ($25J/cm^2$) of irradiation, can minimize possible side effects.[14, 15]

Focal laser photocoagulation can seal the leak seen on FA and achieve resolution of the subretinal fluid in CSCR.[16] However, the conventional focal photocoagulation can cause central or paracentral scotomas, contrast sensitivity loss, accidental foveal damage, retinal distortion, or CNV.[17] Non-thermal subthreshold micropulse diode and yellow lasers have been reported as effective nondestructive treatment options for both subfoveal and extrafoveal lesions in CSCR, with less or no significant retinal damage discernable postoperatively. [18-21] Multiple and overlapping spots with no visible clinical end point are delivered to the areas of diseased RPE, inducing a biological response that promotes the recovery and restoration of the outer blood–retinal barrier and ultimately, the resorption of the subretinal fluid. [22]

This randomized controlled pilot clinical trial aims to compare the efficacy and safety of half-dose PDT and subthreshold micropulse yellow (577-nm) laser in CSCR.

Research plan and methodology

Study Design and Patient Recruitment

Design: prospective, double-masked, randomized controlled interventional study

Study sites
Prince of Wales Hospital (PWH), Shatin
Hong Kong Eye Hospital, Kowloon

Study period
Recruitment period 1/1/2016 – 31/12/2016
Total study period 1 year

The study protocol complies with the Declaration of Helsinki (version 2000) guidelines. Informed consent will be obtained from all participating patients.

Sample size
120 patients
60 patients from Prince of Wales Hospital
60 patients from Hong Kong Eye Hospital

Study subjects

Subjects with chronic central serous chorioretinopathy (CSCR)
Patients with CSCR attending at Prince of Wales Hospital Eye Centre and Hong Kong Eye Hospital between January 2016 and December 2016 will be recruited in the study. If both eyes meet the inclusion criteria, only the right eye will be included in bilateral cases.

Inclusion criteria
(1) CSCR is defined by idiopathic, single, or multiple serous detachments of the neurosensory retina in the macular area associated with RPE changes or RPE leaks on fluorescein angiography (FA) and visual symptoms for less than 3 months(acute CSCR) or more than 3 months (chronic CSCR)
(2) Patient with 18 years or older
(3) Absence of spontaneous resolution or improvement induced by empirical treatment such as acetazolamide or ketoconazole
(4) Presence of written informed consent

Exclusion criteria
(1) Any previous treatment, including PDT and focal thermal laser photocoagulation, for CSCR
(2) Iatrogenic CSC caused by corticosteroids
(3) FA or ICGA findings of CNV, polyploidal choroidal vasculopathy (PCV)

(4) Other maculopathy on clinical examination, FA, indocyanine green angiography (ICGA)
(5) Media opacity such as cataract that could interfere with adequate acquisition of OCT, FA and ICGA images

Randomization and masking

This will be a prospective, double-masked, randomized controlled study. Patients will be randomized into the half-dose PDT group or the subthreshold micropulse yellow (577-nm) laser group at a ratio of 1:1. The randomization sequence will be generated using a computerized randomization table kept centrally by a research assistant. All patients and investigators will be masked to the treatment allocation group. Assessors performing the follow-up assessments also will be masked to the patient allocation group. In the micropulse laser group, 30 ml normal saline will be infused instead of verteporfin, before application of micropulse laser. The infusion syringes will be wrapped externally with aluminum foil. After treatment, all patients will be given protective spectacles and will be instructed to avoid strong light for 3 days.

Half-dose Photodynamic therapy
The PDT will be performed using half-dose verteporfin (Visudyne; Novartis AG, Bülach, Switzerland). For this, 3 mg/m^2 of verteporfin will be infused over 10 minutes, and 15 minutes after beginning the infusion, the laser treatment will be begun. The total light energy delivered to the area of hyperpermeability is 50 J/cm^2 over 83 seconds. The area of irradiation will be set to cover the hyperfluorescent area measured in the images recorded during the middle to late phases of ICGA.

S**ubthreshold micropulse yellow laser**

The focal leaking points and areas of hyperpermeability shown in pretreatment FA and ICGA will be used to guide the subthreshold micropulse laser therapy with 577nm yellow laser (IRIDEX IQ 577 laser, USA) delivered through the PDT laser lens (Volk Optical Inc, Mentor, OH, USA). Micropulse laser with spot size of 200 μm, 0.2 s exposure time, 400mW, a duty cycle of 5%, will be applied in 7x7 treatment grid pattern over areas of focal and diffuse RPE leak, using TxCellTM Scanning Laser Delivery System.

Data collection for all recruited subjects

Baseline and follow-up examinations
Patients will be assessed at baseline and followed up at 1, 3, 6, 9 and 12 months after the treatment. At the baseline and all post-treatment visits, best-corrected visual acuity (BCVA), will be measured with the Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution (logMAR) chart at 4 m. FA and ICGA will be obtained using a confocal laser scanning system (HRA-2, Heidelberg Engineering, Heidelberg, Germany). The optical coherence topography (OCT) (Topcon DRI OCT, Triton OCT, Japan; Spectralis OCT,

Heidelberg Engineering Inc., Heidelberg, Germany) and microperimtery will be performed before the treatment as well as at each clinical visit. Patients with persistent subretinal fluid will have further FA and ICGA performed as decided by the assessors.
Retreatment will be considered if the patients meet two of the three following criteria: decreased visual acuity of at least one line from baseline, presence of subretinal fluid on OCT, and significant leakage on angiography.
Patients in the PDT group will be considered for retreatment every 6 months whereas patients in the micropulse laser group will be considered for retreatment every 3 months. Patients who have persistent SRF after 3 treatments of micropulse laser will receive half-dose photodynamic therapy as rescue therapy, 3 months after the third micropulse laser treatment. In the PDT group, patient who have persistent subretinal fluid 6 months after the initital treatment will receive second half-dose photodynamic therapy.

Outcome Measures, Sample Size Calculation, and Data Analysis
The primary outcome of the study is the proportion of eyes with complete absorption of subretinal fluid (SRF) at 12 months. Secondary outcome measures included serial changes in logMAR BCVA, central foveal thickness, OCT morphological features, microperimetry sensitivity, FA, and ICGA. Other outcomes include the time needed for a complete resolution of the SRF after the primary treatment, the time to a recurrence of an SRF, systemic and ocular complications during the study. A recurrence is defined as the appearance of a new SRF in the OCT images after disappearance following the initial treatment. The absorption of coexistent pigment epithelial detachments (PEDs) will also be evaluated.

Statistical analysis was performed using SPSS software version 20.0 (SPSS, Inc., Chicago, IL). Analysis is performed as intention to treat. Comparisons of categorical variables between the 2 groups are performed using the chi-square test or the Fisher exact test, and continuous variables are compared using a 2-tailed t test or Mann–Whitney U test. A P value of ≤ 0.05 is considered as statistically significant.

Sample size calculation
With an estimated rate of complete subretinal fluid absorption rate at 12 months of 90% for the photodynamic therapy group and 70% for the micropulse laser group, α of 0.05, and power of 80%, and a default rate of 10%, the calculated sample size was a total of 116 patients (58 patients in the photodynamic therapy group and 58 patients in the micropulse laser group).

Patients' privacy and rights

All measurements generated from clinical examinations and imaging in this study will be duplicated into 2 identical sets. One set, in printed hardcopy format, will be kept in the patients' Hospital Authority medical records. The other set, in both electronic and hardcopy formats, will be filed securely in the Clinical

Research Offices of the Department of Ophthalmology & Visual Sciences at the Chinese University of Hong Kong. Electronic version will be kept in password-protected hard-drives and hardcopies will be filed in locked cabinets.

Subjects can withdraw their consents from the study at any time. In the event of patient withdrawal, all clinical data of that particular patient will be deleted and eliminated from the files of the Clinical Research Office. The clinical data in the medical records will, however, be retained for clinical management.

The issue of confidentiality is the major ethical issue, and will be solved by recording the data in a manner that does not allow the participants to be identified (ie. using a non-recognizable code for each patient). A review of medical records that have been already recorded as part of clinical care, therefore this poses no physical risks.

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