

# Choroidal changes in eyes treated with high-dose systemic corticosteroids for optic neuritis

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## Abstract

• **AIM:** To analyze the effect of systemic high-dose corticosteroid on the choroid in patients with unilateral optic neuritis.

• **METHODS:** A retrospective comparative cohort study. Seventy-six eyes of 38 patients with unilateral optic neuritis that received systemic high-dose corticosteroid treatment were enrolled. Choroidal thickness (CT) and choroidal vascularity index (CVI) were measured in both affected and the fellow eyes at baseline, 1wk, 1 and 3mo. Changes in CT and CVI were analyzed in both eyes and compared between eyes.

• **RESULTS:** The mean CT and CVI were 349  $\mu$ m and 0.70 in the affected eyes and 340  $\mu$ m and 0.69 in the fellow eyes at baseline ( $P=0.503$  and  $0.440$ , respectively). Decrement of CT and CVI at month 3 were significant in affected eyes ( $P=0.017$  and  $P<0.001$ ). Decreased CVI began 2wk after treatment whereas CT decreased from 1mo. The CVI also decreased significantly in fellow eyes at 3mo compared to the baseline ( $P=0.001$ ).

• **CONCLUSION:** A significant decrement in CT and CVI can appear after 3mo in optic neuritis patients treated with high-dose systemic corticosteroid treatment. The decrease in CVI appeared earlier than the decrease in CT, suggesting choroidal vasoconstriction caused by systemic steroid as a possible mechanism.

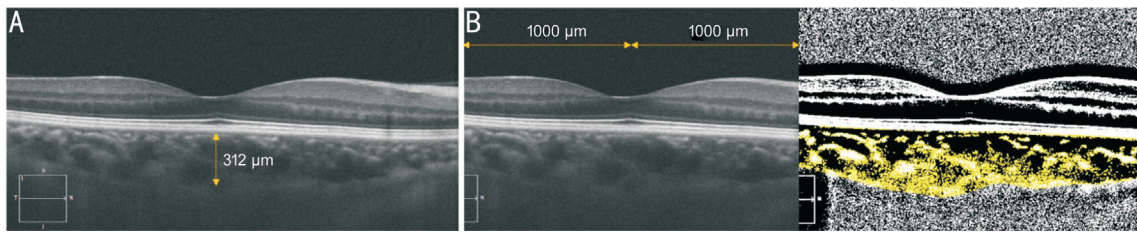
• **KEYWORDS:** corticosteroid; optic neuritis; choroidal thickness; prednisolone

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## INTRODUCTION

Optic neuritis is an inflammatory condition of the optic nerve characterized by a sudden onset of unilateral visual loss<sup>[1-2]</sup>. Visual loss, ranging from a slight deficit in the field of vision to complete loss of light perception, can typically be followed by spontaneous improvement over several months. The value of systemic corticosteroid treatment for this condition had been investigated in the Optic Neuritis Treatment Trial (ONTT)<sup>[3-4]</sup>. This multicenter randomized prospective trial revealed that intravenous methylprednisolone followed by oral prednisone speeds the recovery of visual loss due to optic neuritis and results in slightly better vision at 6mo. The effect of corticosteroids on choroidal thickness (CT) remains controversial. Exogenous as well as elevated endogenous corticosteroids are well-known predisposing factors for central serous chorioretinopathy (CSC)<sup>[5-8]</sup>. The pathophysiology of CSC involves choroidal circulation disturbance manifested as choroidal vascular hyperpermeability (CVH) or choriocapillaris hypoperfusion<sup>[9-10]</sup>. The use of a high dose of systemic corticosteroid can affect the metabolic ability by altering the levels of catecholamine in the blood, which is known as a risk factor for CVH<sup>[11]</sup>. It may also affect the function of the blood-retinal barrier and the osmotic pressure of the choroidal vessels, both of which can cause increased permeability of the choriocapillaris<sup>[12]</sup>. The positive correlation between CVH and CT has been well-established in studies using enhanced depth imaging (EDI) optical coherence tomography (OCT)<sup>[13-14]</sup>. Corticosteroids are suspected to increase CVH in the pathogenesis of CSC, and this may lead to an increment in CT, especially when administered intravenously at a high-dose. However, there is limited information on this theory. Only one study has investigated changes in CT after systemic administration of corticosteroids and reported that the effect of steroid on choroid was found in a selective patient<sup>[15]</sup>. This study included a small number of patients with various diagnoses requiring steroid treatment. We realized the necessity for a study that analyzed the effect of systemic



**Figure 1 Measurement of CT and CVI in EDI OCT** A: Subfoveal CT was obtained using EDI OCT. CT was measured as the distance between Bruch's membrane and the choroid-scleral interface. B: The subfoveal choroidal area with a width of 3 mm, centered at the fovea, was selected using a Polygon selection tool and the TCA was marked. Image binarization was done using the Niblack auto local threshold tool. The selected region was added to the region of interest (ROI) manager. By using the color threshold, LA (arrow) was selected and subsequently added to the ROI manager. The LA appeared as an area of dark pixels and the stromal area as an area of light pixels. CVI was calculated by dividing the LA by the total circumscribed subfoveal choroidal area.

high-dose corticosteroid on the choroid and investigated the changes of CT and choroidal vascularity (CV)<sup>[16-17]</sup> before and after systemic high-dose corticosteroid treatment, in a singular disease group of optic neuritis.

### SUBJECTS AND METHODS

**Ethical Approval** This retrospective, observational study was conducted at Bucheon St. Mary's Hospital in Seoul, South Korea, between January 2015 and December 2017. This study was approved by the Institutional Review Board of the Bucheon St. Mary's Hospital, which waived the written informed consent because of the study's retrospective design and was conducted in accordance with the tenets of the Declaration of Helsinki.

**Patients** We retrospectively analyzed 38 patients who were diagnosed with unilateral optic neuritis and had been treated with systemic corticosteroids. The diagnosis criteria and exclusion criteria for optic neuritis were based on the ONTT study<sup>[4]</sup>. Patients were diagnosed with optic neuritis when acute or subacute unilateral blindness, relative abducted pupillary defects, color blindness, pain during ocular motility, and visual field defects were present, and those who visited the hospital within 7d of symptom onset were included. Patients showing other neurological signs and symptoms were excluded to reduce the possibility of other causes for optic nerve inflammation. In addition, patients with other systemic disease or ocular disease (*e.g.* glaucoma or disease of the retina and choroid), recurrent optic neuritis, other suspected causes of optic nerve inflammation (*e.g.* ischemic, genetic, or traumatic), taking medication which can affect the optic nerve or choroid, and optic atrophy were excluded.

All patients underwent thorough ophthalmologic examinations of both eyes including slit-lamp microscopy, automatic refraction (Canon RK-I autorefractometer; Canon, Tokyo, Japan), intraocular pressure (IOP) using a Goldman applanation tonometer, fundus examination, and high definition (HD) OCT (Cirrus-HD 4000, Carl Zeiss Meditec, Jena, Germany) at the baseline. Intravenous systemic corticosteroid treatment was

started within 6h after the diagnosis of optic neuritis: 250 mg of methylprednisolone was administered at intervals of 6h four times a day for 72h for a total of 12 times. Systolic and diastolic blood pressure and blood glucose were measured 1h after the administration of systemic corticosteroid, and the mean and standard deviation were calculated at 24-hour intervals for 3d during the corticosteroid administration. Ophthalmic examinations were performed at the time of diagnosis, and 2wk, 1, and 3mo after the treatment.

**Measurement of Subfoveal Choroidal Thickness and Choroidal Vascularity Index** An HD line scan intersecting the fovea using the EDI mode of HD OCT was used for the CT and choroidal vascularity index (CVI) analysis. All measurements were performed twice by the same examiner at two different time points. CT was measured at the subfoveal area from the retinal pigment epithelium to the outer border of the choroid using software-based calipers<sup>[18]</sup>.

A raster scan passing through the fovea was selected for image binarization. We adapted the image segmentation technique proposed by Sonoda *et al*<sup>[19]</sup>. Briefly, after binarization of the OCT line scan with the Niblack local threshold method using Image J software (version 1.51; <https://imagej.nih.gov/ij/>), the total choroidal area (TCA) was marked by selecting the subfoveal choroidal area within a width of 1500 μm. The luminal area (LA) was indicated by an area of dark pixels and the stromal area was indicated by an area of light pixels within the TCA. The TCA, LA, and stromal area were calculated. CVI was calculated by dividing the LA by the TCA (Figure 1).

**Statistical Analysis** All statistical analyses were performed using IBM SPSS ver. 22.0 software (IBM Corp., Armonk, NY, USA). The Student's *t*-test was used to compare continuous variables among affected and fellow eyes. The Mann-Whitney test was used when a normal distribution could not be confirmed. Follow-up measurements of macular thickness, CT, and CVI after 72h of systemic corticosteroid treatment were analyzed by repeated-measures analysis of variances (RM-ANOVA). Snellen visual acuity was converted to logarithm

**Table 1** Baseline characteristics of study eyes

Clinical factors	Total eyes	Affected eyes	Fellow eyes	mean±SD (range)
				<i>P</i> <sup>a</sup>
Age (y)	46.8±20.0 (14-82)			
Gender (male/female)	14/24			
Diabetes, <i>n</i> (%)	6 (16)			
Hypertension, <i>n</i> (%)	6 (16)			
Systolic blood pressure (mm Hg)	119.7±14.2 (90-160)			
Diastolic blood pressure (mm Hg)	73.8±10.5 (60-100)			
Random glucose (mg/dL)	148.4±50.8 (78-331)			
Refractive errors (Diopters)	-1.13±1.69 (-5.88 to 2.25)	-1.12±1.62 (-5.88 to 2.13)	-1.15±1.77 (-5.13 to 2.25)	0.938
BCVA (logMAR)	0.60±0.88 (0-3.70)	1.04±0.93 (0.00-3.70)	0.03±0.07 (0.99-0.22)	<0.001 <sup>b</sup>
Initial IOP (mm Hg)	13.9±2.5 (10-22)	13.9±2.6 (10-22)	13.9±2.4 (10-19)	0.928

SD: Standard deviation; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure. <sup>a</sup>*t*-test between affected and fellow eyes; <sup>b</sup>Statistically significant *P*-value.

of minimal angle resolution (logMAR) units for the statistical analysis.  $P < 0.05$  were considered statistically significant.

## RESULTS

In total, 76 eyes of 38 patients diagnosed with unilateral optic neuritis were included in the study. The mean age of patients was 46.8±20.0y, of which 37% were male. Prevalence of diabetes and hypertension were both 16% in these patients. The mean logMAR visual acuity was 1.04±0.93 in the affected eyes and 0.03±0.07 in the fellow eyes ( $P < 0.001$ ). Baseline demographics and clinical characteristics are summarized in Table 1.

No significant changes in blood glucose level and systolic/diastolic blood pressure were observed during the 3d of systemic corticosteroid treatment ( $P = 0.113$ , 0.983, and 0.060, respectively; Figure 2A and 2B). Visual acuity improved significantly during the first month after treatment in affected eyes ( $P < 0.001$ ), with a decrease in the macular thickness which did not reach statistical significance ( $P = 0.057$ ; Figure 3A and 3B).

The mean CT and CVI were 349  $\mu$ m and 0.70 in the affected eyes and 340  $\mu$ m and 0.69 in the fellow eyes at baseline ( $P = 0.503$  and  $P = 0.440$ ). RM-ANOVA revealed a significant change in the CT and CVI in affected eyes ( $P = 0.017$  and  $P < 0.001$ , respectively; Figure 4A and 4B). In post-hoc analysis, CT did not change from baseline until 1mo, but the change from 1mo to 3mo was significant ( $P = 0.011$ ) in affected eyes. The decrease in CVI started from 2wk after the treatment to 3mo ( $P = 0.005$  and 0.001 at 1 and 3mo, respectively). The CVI also decreased significantly in fellow eyes at 3mo compared to the baseline ( $P = 0.001$ ).

## DISCUSSION

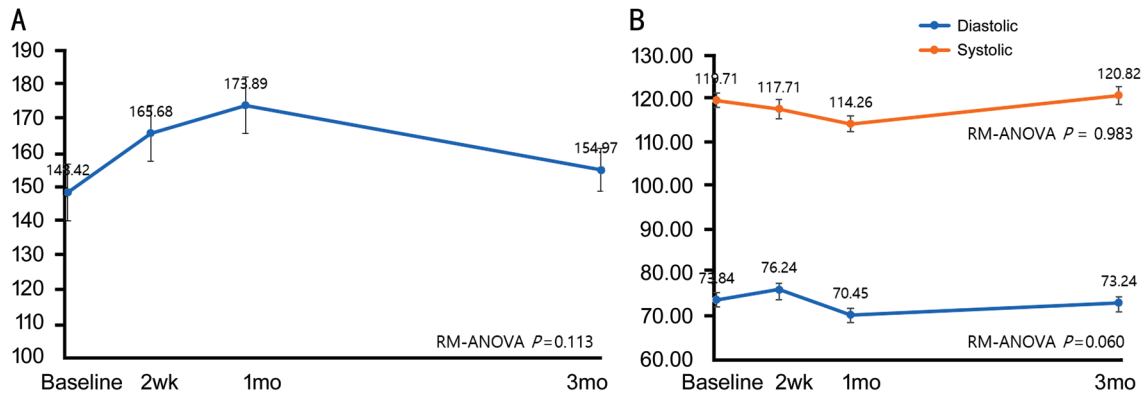
In this study, changes in the thickness and vascularity of the choroid were analyzed after systemic high-dose corticosteroid for optic neuritis. We found that there was a significant

decrement in CT and CVI at 3mo after treatment. The decrease in CT began 1mo after the treatment whereas CVI started to decrease earlier at 2wk. In addition, CVI decrement was also evident in fellow eyes, which did not suffer optic neuritis. To the best of our knowledge, this is the first study to report CT change at 3mo after systemic high-dose corticosteroid therapy in optic neuritis eyes. By enrolling unilateral optic neuritis, which accounts for most of the optic neuritis cases, and by comparing affected and fellow eyes, this study demonstrates the effects of systemic high-dose corticosteroid on choroidal morphology as well as the effect of the disease itself.

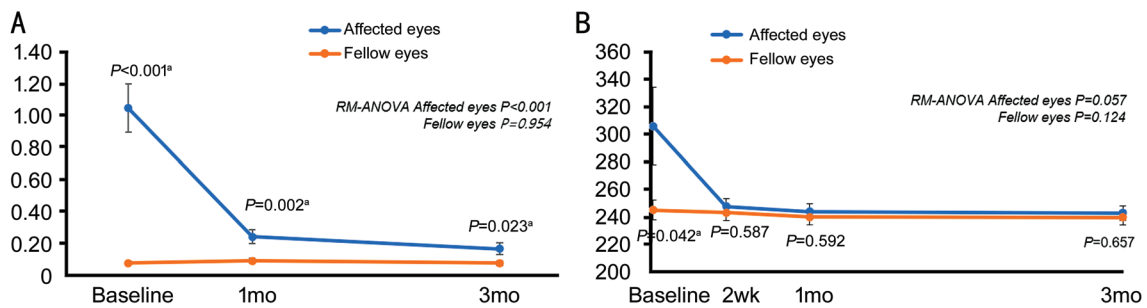
So far, few studies have investigated choroidal changes after optic neuritis. Park *et al*<sup>[20]</sup> revealed a difference in the pattern of association between patients with optic atrophy and normal eyes, suggesting that optic atrophy caused by acute idiopathic optic neuritis could affect the pattern of association between peripapillary retinal nerve fiber layer thickness and macular CT. However, they reported no difference in CT between optic atrophy patients and normal controls. The important differences between the current study and the Park's study<sup>[20]</sup> are in the control group (fellow eyes vs healthy controls), treatment method (high-dose steroid vs unknown), and duration of the condition (3mo vs unknown). These differences might have caused the differences in the CT results.

In accordance with the report from Maruko *et al*<sup>[21]</sup> eyes with optic neuritis did not show a significant change in CT for 1mo after steroid treatment. However, CT decreased at 3mo in affected eyes. This implies some latency in the change of CT in optic neuritis after steroid treatment. Although the value did not reach statistical significance, fellow eyes revealed a similar tendency, which means that the change in CT might be systemic at some level.

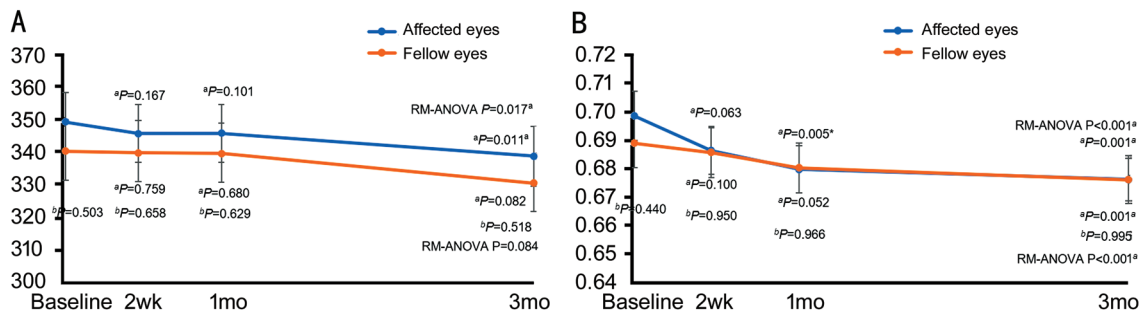
CVI, which indicates the proportion of vascular area and



**Figure 2** Changes in blood glucose level (A) and blood pressure (B) during systemic high-dose corticosteroid treatment. No significant changes in blood glucose level and systolic/diastolic blood pressure were observed during the 3d of systemic corticosteroid treatment.



**Figure 3** Changes in visual acuity (A) and central macular thickness (B) during the 3mo follow-up period. Visual acuity improved significantly in affected eyes during the first month after treatment. The decrease in macular thickness did not reach statistical significance. <sup>a</sup> $P < 0.05$ .



**Figure 4** Changes in CT (A) and CVI (B) during the 3mo follow-up period. The mean CT and CVI did not differ through the entire follow-up period between affected and fellow eyes. Decreases in the CT and CVI were significant in affected eyes. CT did not change from baseline to 1mo, but the change from 1mo to 3mo was significant in affected eyes. The decrease in CVI started from 2wk after treatment to 3mo in affected eyes. The CVI also decreased significantly in fellow eyes at 3mo compared to the baseline. <sup>a</sup>Comparison between baseline and each time point; <sup>b</sup>Comparison between affected and fellow eyes.

stromal area, also showed a decrement in both eyes at 3mo after steroid treatment. This can be interpreted as a decrease with time in vascular components, rather than stromal components, in these eyes, therefore, vascular components are responsible for the decreased CT. In addition, the decrease in CVI started earlier than the decrease in CT. A decrease in choroidal vessel caliber may proceed a decrease in total volume. The decrement of the CVI during the 3-month follow-up period was demonstrated in fellow eyes at a significant level, although the decrement was more prominent in affected

eyes, suggesting that a CVI change might have resulted from both disease status and systemic high-dose steroids. Systemic corticosteroids have been considered to affect the choroidal vessels in several studies. Han *et al*<sup>[15]</sup> studied the effect of systemic steroids on CT in 18 patients treated systemically with a high-dose corticosteroid for various diseases (including Tolosa-Hunt syndrome, multiple sclerosis, and neuromyelitis optica), and reported no CT change at 1mo, but one patient developed CSC with increased CT. Ambiya *et al*<sup>[22]</sup> reported that CT did not differ between steroid-induced

CSC and idiopathic CSC. The slightly higher CVI in steroid-induced CSC compared to idiopathic CSC, thereby implying that choroidal vessel dilatation and hyperpermeability are common mechanisms in steroid-induced and idiopathic CSC. On the other hand, Honda *et al*<sup>[23]</sup> reported that eyes with steroid-induced CSC have thinner choroid compared to idiopathic CSC eyes, suggesting a complex mechanism for CSC in steroid-induced CSC eyes. In this study, CT did not change for 1mo but both CT and CVI decreased in the 3mo after systemic steroid treatment, suggesting the use of high-dose systemic steroids may cause a decrease in CT and CVI in the long term.

A number of mechanisms can explain how corticosteroids affect choroidal vessels. Direct increase in the permeability of the blood vessels might also occur, together with retinal pigment epithelial cell tight junction damage<sup>[24]</sup>. This may cause a temporary increase in CT. However, in this study, as well as in previous studies, CT did not increase during steroid treatment or at 1mo and decreased thereafter. Hyperpermeability caused by the steroids may not have a significant effect on CT. Corticosteroids could also induce choroidal vasoconstriction by reducing nitric oxide production<sup>[25]</sup>. This may explain the decrease in the CVI following systemic steroid treatment in this study. CT decrement at 3mo may be followed by a decrease in CT.

This study has limitations inherent to its retrospective nature. Excluding patients without good imaging data with regular follow-up might have caused bias. In addition, the relatively short follow-up period of this study requires further validation with a study of a longer follow-up period. However, this is the first study to analyze choroidal morphology change after high-dose systemic corticosteroid use in a single disease group of optic neuritis, in which other systemic or ocular conditions are controlled.

In conclusion, a significant decrement in CT and CVI can appear after 3mo in optic neuritis patients treated with high-dose systemic corticosteroid treatment. The decrease in CVI appeared earlier than the decrease in CT, suggesting choroidal vasoconstriction caused by systemic steroids might be the reason for the result in this study. Further studies with longer follow-up period and larger sample sizes are warranted to validate the result of this study.

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**Authors' contributions:** Baek J: Conception, design of the study, providing and assembly of data, writing of manuscript text, preparing figures, review of the manuscript. Lee JY and Lee JH: Collection and assembly of data, data analysis and interpretation, preparation and review of the manuscript. Ra H and Kang NY: Providing and assembly of data, preparation and review of manuscript.

**Conflicts of Interest:** Lee JH, None; Lee JY, None; Ra H, None; Kang NY, None; Baek J, None.

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