Changes in Choroidal Thickness After Systemic Administration of High-Dose Corticosteroids: A Pilot Study

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PURPOSE. To characterize the effects of corticosteroids on choroidal thickness, we measured the choroidal thickness in patients treated systemically with a high-dose corticosteroid.

METHODS. A prospective, pilot study was conducted on 20 patients who required high-dose corticosteroid pulse therapy (>500 mg/d). Choroidal thickness was measured at baseline, 1 day, 1 week, and 1 month after corticosteroid administration. Blood pressure was measured four times a day for the first 5 days of steroid treatment.

RESULTS. This study ultimately included 35 eyes from 18 patients. Each patient was treated with high-dose corticosteroid therapy at a concentration of 19.5 ± 4.1 mg per kg body weight for 5.2 ± 1.1 days. Mean subfoveal choroidal thickness at baseline was 259.8 μm (range, 86.4–394.7 μm). Choroidal thickness showed no significant change at 1 day, 1 week, or 1 month after corticosteroid administration (P = 0.197). Mean systolic blood pressure increased by 13 mmHg (P = 0.008), but diastolic pressure did not change (P = 0.117). One patient (5.6%) who had presented with pigment epithelial detachment (PED) and thick choroid (381.1 μm) develop bilateral focal subretinal fluid during the study and showed central serous chorioretinopathy (CSC) with a 1.3% increase in subfoveal choroidal thickness.

CONCLUSIONS. No consistent changes in choroidal thickness were observed after systemic high-dose corticosteroid treatment, but one patient with PED and thick choroid showed an increase in choroidal thickening as well as features of CSC. Thus, steroid-induced CSC may be an idiosyncratic response in selected vulnerable individuals rather than a dose-dependent effect.

Keywords: central serous chorioretinopathy, choroid, glucocorticoid, optical coherence tomography, prednisolone

The pathophysiology of central serous chorioretinopathy (CSC), first reported by Graefes1 in 1886, remains to be elucidated.2–4 Patients with CSC often exhibit choroidal vascular hyperpermeability and abnormal choroidal circulation, and research has shown that the choroid plays an important role in the pathophysiology of CSC.5,6 Recently, enhanced depth imaging (EDI) technology has made it possible to measure choroidal thickness in vivo. The associated findings have shown increased choroidal thickness in patients with CSC.7–9

The relationship between corticosteroid administration and the development, recurrence, and worsening of CSC has been reported in several case series.10–12 Some features that differentiate corticosteroid-associated CSC from idiopathic CSC include reduced male predominance, increased bilaterally, more frequent recurrences, and a higher prevalence of variant CSC.13 Notably, the daily dosage of prednisolone has a greater influence on the onset of CSC than does the total dose.14

Therefore, corticosteroid administration may increase choroidal thickness and thereby induce the development of CSC. Currently, however, there are no data on changes in choroidal thickness among patients treated with corticosteroids or on the incidence of steroid-induced CSC in a healthy population.

The present study was carried out to determine the effects of high-dose corticosteroid treatment on choroidal thickness. Understanding how the choroid responds to systemic corticosteroid treatment may elucidate the pathophysiology of CSC. To the best of our knowledge, this is the first prospective study to obtain serial measurements of choroidal thickness in patients treated systemically with high-dose corticosteroids.

METHODS

Subjects

This pilot prospective study was performed on patients who required corticosteroid pulse therapy (>500 mg/d) and oral maintenance therapy for any disease that involved neither the retina nor the choroid. The 20 patients enrolled in our study presented for corticosteroid pulse therapy at Seoul National University Bundang Hospital during the period from October 2011 to March 2012. Informed consent was obtained from each patient before enrollment. The institutional review board of Seoul National University Bundang Hospital approved the study protocol. We also adhered to the tenets of the Declaration of
Helsinki for the use of human participants in biomedical research throughout the study.

Examinations and Data Collection

Prior to systemic corticosteroid administration, patients underwent full ophthalmologic examinations including refraction, best-corrected visual acuity (BCVA; Snellen chart) assessment, slit-lamp biomicroscopy, indirect fundoscopy, axial length measurement using an IOLMaster (Carl Zeiss, Jena, Germany), and spectral-domain optical coherence tomography (SD-OCT, Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). Ophthalmologic examinations were repeated at 1 day, 1 week, and 1 month after the initial administration of high-dose systemic corticosteroids.

The standard protocol for obtaining EDI-OCT images was reported previously (Fig. 1).15,16 The choroid was imaged by positioning an OCT device close enough to the eye to obtain an inverted image. The resultant images were viewed and measured using Heidelberg Eye Explorer software (version 1.7.0.0; Heidelberg Engineering). Measurements of choroidal thickness began at the outer portion of the hyperreflective line corresponding to the RPE and extended to the inner surface of the sclera. Subfoveal region measurements were obtained manually using the calipers software tool (Heidelberg Eye Explorer software). These measurements were performed by a single retinal specialist (JMH). The grader was masked to the diagnosis. Eyes were excluded if they had any history of previous photodynamic therapy (PDT), intravitreal injections, macular surgery, focal laser treatment, myopia of more than 6 diopters (D) or axial length more than 26.5 mm, amblyopia, glaucoma, any disease that causes distortion of the central macula (e.g., epiretinal membrane), any type of macular degeneration, proliferative retinopathy of any type, uncontrolled diabetes or hypertension, any retinovascular abnormality, or any evidence of current CSC. Any patient under treatment with corticosteroids at the time of presentation to our institution was excluded from the study.

Each patient’s medical history was investigated. The data collected included information on the presence of hypertension, diabetes, and/or other underlying diseases, as well as current treatment with any medication. We measured blood pressure four times a day (7 AM, 12 PM, 3 PM, and 7 PM). These measurements were used to calculate average daily blood pressure. Blood pressure was checked repeatedly for 5 days after the initial dose of corticosteroids.

Statistical Analysis

A linear mixed model was used to analyze differences in choroidal thickness. The Wilcoxon signed-rank test was used to compare blood pressure measurements. A P value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using R 2.15.2 ([in the public domain] http://www.r-project.org; R Core Team, Vienna, Austria) and SPSS 18.0 software for Windows (SPSS Inc., Chicago, IL USA).

RESULTS

Demographic and Clinical Characteristics

Among the 20 patients who were initially enrolled, 18 (90%) attended all follow-up examinations. The other two patients for whom complete follow-up was not feasible were excluded from the analysis. Among 36 eyes from these 18 patients, one eye that exhibited unilateral myopia (>6 D) was excluded. There was no indication in any eye requiring steroid therapy that might have had an effect on the choroid, specifically, those associated with central serous chorioretinopathy, Vogt-Koyanagi-Harada diseases, choroiditis, scleritis, and polypoidal choroidal vasculopathy, and so on. Ultimately, 35 eyes from 18 patients were eligible. Mean patient age was 47.7 ± 12.0 years (range, 31–70 years), and 7 patients (38.9%) were female. The mean BCVA (logMAR) was 0.08 ± 0.16 (0.83). Mean refractive error in spherical equivalent was −1.7 ± 2.0 D. Mean axial length was 24.4 ± 1.3 mm. Four patients had hypertension and two patients had diabetes; all cases were well controlled with medication. The indication for corticosteroid therapy was Tolosa-Hunt syndrome in six patients, multiple sclerosis in three patients, neuromyelitis optica in
Effect of Corticosteroids on Choroidal Thickness

TABLE. Patient Demographic and Ocular Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>18</td>
</tr>
<tr>
<td>Age, y</td>
<td>47.7 ± 12.0 (range, 31–70)</td>
</tr>
<tr>
<td>Sex, female</td>
<td>7 (38.9%)</td>
</tr>
<tr>
<td>BCVA, logMAR</td>
<td>0.08 ± 0.16</td>
</tr>
<tr>
<td>Spherical refractive error, D</td>
<td>−1.7 ± 2.0</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>24.4 ± 1.3</td>
</tr>
<tr>
<td>Underlying diseases</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Indications for corticosteroid therapy</td>
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</tr>
<tr>
<td>Tolosa-Hunt syndrome</td>
<td>6 (33.3%)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td>Neuromyelitis optica</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>Recurrent myelitis</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>Active TAO</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>Acute transverse myelitis</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>Recurrent vestibular neuritis</td>
<td>1 (5.6%)</td>
</tr>
<tr>
<td>Corticosteroid administration</td>
<td></td>
</tr>
<tr>
<td>Daily dose,* mg/kg</td>
<td>19.5 ± 4.1 (range, 11.6-27.2)</td>
</tr>
<tr>
<td>Duration, d</td>
<td>5.2 ± 1.1 (range, 3-8)</td>
</tr>
<tr>
<td>Type of corticosteroid</td>
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<tr>
<td>Methylprednisolone</td>
<td>17 (94.4%)</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>1 (5.6%)</td>
</tr>
</tbody>
</table>

* Corticosteroid dose was converted to the prednisolone equivalent, given in milligrams per kilograms body weight.

Among the 35 eyes included in the study, average subfoveal choroidal thickness prior to corticosteroid administration was 259.8 ± 90.6 μm (range, 86.4–394.7 μm). After steroid administration, choroidal thickness was measured as 253.9 ± 88.9 μm (97.7%, as compared with baseline values), 264.5 ± 95.4 μm (101.8%), and 260.2 ± 95.2 μm (100.2%) at 1 day, 1 week, and 1 month after high-dose corticosteroid administration, respectively (Fig. 2). Thus, steroid administration had no significant effect on choroidal thickness (P = 0.197, linear mixed model).

Blood Pressure Changes Following Corticosteroid Administration

The changes in blood pressure observed following the administration of corticosteroids are presented in Figure 4. Baseline systolic blood pressure was 122.2 ± 13.8 mmHg and increased to 128.7 ± 16.1, 125.1 ± 12.0, 130.8 ± 13.6, 132.9 ± 17.4, and 135.1 ± 17.7 mmHg in the 5 days after corticosteroid administration (Wilcoxon signed-rank test, P = 0.006, 0.163, 0.004, 0.023, and 0.008, respectively). Diastolic pressure was 70.5 ± 10.0 mmHg at baseline, with no change after corticosteroid administration (Wilcoxon signed-rank test, P = 0.887, 0.327, 0.394, 0.215, and 0.117, respectively). Pre- and posttreatment blood pressure measurements for Case 17 were similar to those obtained for the other 17 patients (P = 0.599, systolic blood pressure; P = 0.241, diastolic blood pressure; linear mixed model).

Discussion

Various theories regarding the pathophysiology of CSC have highlighted the importance of the choroidal circulation. The choroidal tissue in eyes with CSC is thought to have abnormal permeability due to stasis, ischemia, or inflammation.17 As inferred from the results of indocyanine-green angiography5,6 and EDI-OCT7 Hyperpermeable choroidal vessels are thought to increase the hydrostatic pressure of choroidal tissue, which leads to the formation of PEDs, creating small breaks in the integrity of the RPE, and leading to the accumulation of fluid between the retina and the RPE.4 Our data suggest that corticosteroid treatment has no effect on choroidal thickness in the typical patient with a condition requiring high-dose corticosteroid therapy. Although most eyes showed no change in choroidal thickness, the eyes of one patient (Case 17) with preexisting PEDs and a thickened choroid at baseline demonstrated increased choroidal thickness as well as serous detachment of the neurosensory retina, suggesting steroid-induced CSC. This result indicates that steroid-induced CSC due to increased choroidal thickness is an idiosyncrasy rather than a dose-dependent response. The characteristics that render an eye vulnerable to steroid-induced CSC remain...
unclear, but may involve predisposing genetic and environmental factors. The application of these findings in clinical practice will require physicians to measure choroidal thickness and identify any preexisting PED prior to systemic corticosteroid administration. Those with thick baseline values of choroidal thickness should be forewarned about the possibility of steroid-induced CSC.

Several studies have shown that choroidal thickness is thicker among patients with CSC as compared with individuals of the general population. Mean subfoveal choroidal thickness in healthy eyes has been documented as 287 ± 76 and 235 ± 67 μm, respectively, as compared with 329.3 ± 83.0 and 505 ± 124 μm² in eyes with CSC. Remarkably, PDT has been proven to reduce subfoveal choroidal thickness in eyes with CSC from 389 ± 106 to 330 ± 103 μm after 1 month of therapy. Among the 32 eyes that exhibited neither PED nor other change in subfoveal choroidal thickness after corticosteroid administration, mean choroidal thickness was 252.4 ± 87.9 μm, which was similar to the choroidal thickness in healthy study participants. However, the mean subfoveal choroidal thickness in Case 17, who developed CSC, was 381.1 μm at baseline and 430.9 μm 1 week after corticosteroid administration. These values are comparable with those obtained previously for eyes with CSC. The increase in subfoveal choroidal thickness was approximately five times that observed in the other 17 patients (11.9% in Case 17 vs. 1.8% in the other patients). This suggests that the development of steroid-induced CSC in Case 17 was associated with the increase in choroidal thickness. As Case 17 presented with asymptomatic PED and baseline choroidal thickening before steroid exposure, it is also possible that sensitivity to corticosteroids and endogenous hypercortisolism were present prior to corticosteroid pulse administration. The pathogenesis of steroid-induced CSC may involve systemic hypertension induced by systemic corticosteroid administration. Systemic hypertension associated with choroidal vascular dysregulation may increase choroidal hydrostatic pressure, resulting in the accumulation of subretinal fluid. Corticosteroid treatment elevates systolic blood pressure, by as much as 15 mmHg within 24 hours. In this study,
average systolic blood pressure had increased by up to 13 mmHg at 5 days after steroid administration. However, measurements of choroidal thickness in the 35 eyes without baseline choroidal thickening showed no change despite the increase in blood pressure, and none of these eyes developed CSC. Case 17 showed no discernible change in blood pressure during the follow-up period. Therefore, these data do not support a direct correlation between systemic blood pressure and choroidal thickness. Similarly, Li et al. reported that arterial blood pressure had no effect on subfoveal choroidal thickness, whereas Tan et al. reported that changes in choroidal thickness correlated positively with changes in systolic blood pressure.

There are several limitations to our study. First, as a pilot study, the study included a relatively small number of patients. A larger patient population will be required to accurately determine the incidence of steroid-induced CSC, as well as to identify a potential threshold for the use of choroidal thickness to predict the risk of CSC. Second, choroidal thickness can be affected by diurnal variations. Tan et al. reported that choroidal thickness peaks in the early morning and decreases progressively throughout the day. According to our data, OCT measurements were obtained at 2:24 PM (±2.8 hours), 12:35 PM (±2.3 hours), 1:02 PM (±2.2 hours), and 12:27 PM (±2.2 hours) at baseline, 1 day, 1 week, and 1 month after corticosteroid administration, respectively. The change in choroidal thickness over a period of 2 days, as calculated from the data reported by a previous study, was 7.9 µm, which represents 2.1% of baseline choroidal thickness (372.2 µm). However, Case 17 exhibited a 13% change in choroidal thickness. These data suggest that OCT images obtained on different days should nonetheless be taken at the same time of day.

In conclusion, choroidal thickness did not change significantly in most patients treated systemically with high-dose corticosteroids, during or after steroid administration. However, one patient who initially presented with PED and thick choroid developed an increase in the number of PEDs and choroidal thickening. By the end of the study, serous detachment of the neurosensory retina suggesting steroid-induced CSC was noted as well. Our results suggest that steroid-induced choroidal thickening and CSC is an idiosyncratic rather than dose-dependent response to treatment. Further research is warranted to examine the incidence of steroid-induced CSC and to determine the exact cutoff value to be applied when using measurements of choroidal thickness to predict the risk of developing CSC after corticosteroid administration.

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References


