The Fluctuation of Intraocular Pressure Measured by a Contact Lens Sensor in Normal-Tension Glaucoma Patients and Nonglaucoma Subjects

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Purpose: We compared the fluctuation of intraocular pressure (IOP) in normal-tension glaucoma (NTG) patients and individuals with nonglaucoma eyes. We obtained continuous IOP values using a SENSIMED Triggerfish contact lens sensor.

Materials and Methods: The eyes of 12 nonglaucoma subjects and 14 NTG patients were examined. In all 26 subjects, the IOP fluctuation was measured continuously for 24 hours with a contact lens sensor. We evaluated the range of IOP fluctuations over the 24-hour period separately for diurnal IOP and nocturnal IOP and identified each subject’s maximum value. The range of IOP fluctuation was analyzed, cutoff level of IOP fluctuation was calculated using receiver operating characteristic curve analyses.

Results: The mean IOP in the NTG eyes was 11.5 ± 2.4 mm Hg and that in the nonglaucoma eyes was 12.7 ± 2.0 mm Hg, a non-significantly difference (P = 0.175). The 24-hour range of IOP fluctuations in the NTG group was significantly larger than that of the nonglaucoma group (P = 0.007). The percentage of NTG patients who had the peak time of IOP fluctuation during nocturnal sleep was 57.1%, whereas the corresponding rate for the nonglaucoma eyes was 91.7%. The cutoff level of IOP fluctuation for glaucoma was 442 mVeq (sensitivity = 1.00; specificity = 0.571).

Conclusions: The range of IOP fluctuation was larger in the eyes with NTG than in the nonglaucoma eyes. This larger fluctuation might be one of the reasons underlying the aggravation of the visual field by NTG. Measurements of 24-hour continuous IOP might be one of the useful methods to distinguish NTG from nonglaucoma eyes.

Key Words: normal-tension glaucoma (NTG), intraocular pressure (IOP), contact lens sensor (CLS), Triggerfish, fluctuation (J Glaucoma 2016;00:000–000)

Glaucoma is a neurodegenerative disease of the eye, and the leading cause of blindness in Japan. Normal-tension glaucoma (NTG) is typically defined as optic disc and/or visual field glaucomatous changes in an individual who has never shown an untreated intraocular pressure (IOP) value above 21 mm Hg. IOP is a well-known significant risk factor for the progression of glaucoma, and the clinical management of glaucoma patients focuses on lowering their IOP. According to Collaborative Normal Tension Glaucoma study reports, 20% of NTG subjects showed visual field progression despite a reduction in their IOP by > 30% from baseline. In clinical practice, we have encountered some patients whose visual fields were damaged despite their low IOP, suggesting that non-IOP-related elements may be involved in the progression of NTG. The mechanism of progression of NTG has not been fully elucidated.

Several studies showed that large IOP fluctuation might be one of the reasons for glaucoma progression. IOP is known to fluctuate, and as such, our understanding of fluctuation’s behavior over time is essential for patient management and treatment decisions. The dynamic nature of IOP underlines the need for a clinical tool that would allow continuous assessment of 24-hour IOP, especially during the night, when IOP often tends to increase. We hypothesized that 24-hour IOP assessments could provide better information for clinical decision making than only-daytime IOP assessments.

A contact lens sensor (CLS) was developed to continuously monitor habitual IOP fluctuations for 24 hours by measuring changes in the eye’s circumference in the area of the corneoscleral junction. The purpose of the present study was to compare IOP fluctuations in patients with NTG with the fluctuations in nonglaucoma eyes, using a CLS.

MATERIALS AND METHODS

Subjects
This was an observational, cross-sectional study. A total of 26 subjects were enrolled. The control group consisted of 12 nonglaucoma subjects (4 men, 8 women) with a mean age of 68.4 ± 10.9 years. The NTG group consisted of 14 patients (6 men, 8 women) with a mean age of 66.9 ± 9.9 years.

All subjects were recruited at the Toyama University Hospital from March 2012 to May 2015. One glaucoma specialist (N.T.) diagnosed all the cases of NTG and nonglaucoma eyes. All 26 subjects underwent a comprehensive ophthalmic examination including refraction, visual acuity, Goldmann gonioscopy, Goldmann applanation tonometry (GAT), fundus examination, anterior segment optical coherence tomography (AS-OCT) (CASIA SS-1000; TOMEY Corp., Nagoya, Japan), and automated perimetry (Humphrey Field Analyzer, Carl Zeiss Ophthalmic Systems, Dublin, CA).

The research protocol was approved by the Institutional Review Board of the University of Toyama.
Changes in IOP.9-10 The unit of measurement used in monitoring the IOP fluctuation with the Triggerfish is not mm Hg but mVeq (millivolt equivalent), which is unique to the Triggerfish. The median values were monitored for 30 seconds every 5 minutes, providing 288 points over the 24-hour period. The subjects were instructed to record the time when they installed the eye drops, went to bed, and woke up. The subjects did not have any restriction in their posture during the measurement. Patients with NTG glaucoma used their glaucoma medication at the usual time during the measurement period.

Evaluation of IOP Fluctuation and Circadian Pattern

We evaluated the range of IOP fluctuation and the IOP pattern of all 26 subjects. The range of IOP fluctuations, which was defined as the difference between the maximum value (mVeq) and the minimum value during the course of the 24-hour recording, was calculated from the data of IOP fluctuations, and we compared the ranges of the NTG eyes with those of the nonglaucoma eyes.

The subjects were classified into 2 patterns: “diurnal” and “nocturnal.” Nocturnal/sleep periods were distinguished by the presence of blink spikes in IOP fluctuations (Fig. 1). In the diurnal pattern, the average diurnal amplitude value was higher than the average nocturnal amplitude value, and the maximum value was diurnal. In the nocturnal pattern, the average nocturnal amplitude was higher than the average diurnal, and the maximum value was nocturnal. In the unclassifiable group, the average diurnal amplitude was higher than the average nocturnal amplitude, but the maximum value was nocturnal, or the reverse.

We plotted the mean IOP values for each 1-hour period because it was difficult to evaluate the many peaks into spikes using the data from every 5-minute measurement. We defined the peak IOP time as the highest of the mean IOP values for the 1-hour period.

Because changes in corneal shape may potentially affect contact lens–based continuous IOP monitoring, we measured the central corneal thickness (CCT) and corneal curvatures before and after the 24-hour IOP measurement with the AS-OCT.

Statistical Analysis

The paired t test was used to compare the values of the NTG group and nonglaucoma group. The Wilcoxon signed-rank test was used for analyzing the corneal changes before and after CLS measurement. Assuming that the SD (100 mVeq) of the IOP daily variation was 100 mVeq, we found that a total of 10 pairs of value was necessary to detect a meaningful difference of 100 mVeq with respect to the IOP daily variation with 80% power and the 2-sided significance level of 0.05.

We calculated a cutoff level to distinguish glaucoma patients from nonglaucoma subjects using receiver operating characteristic curve analysis.

RESULTS

Ophthalmic Data

Table 1 shows the baseline data of the subjects and the IOP fluctuation data. Age, sex, and CCT showed no significant differences between the NTG and nonglaucoma groups. In the NTG group, 12 of the 14 patients (85.7%)
showed phakia, and 10 of the 12 nonglaucoma subjects (83.3%) showed phakia. The average IOP value from the patients’ eyes treated with eye drops (11.5 ± 2.4 mm Hg) and lowering IOP in the NTG group were not significantly different from the IOP value of the nonglaucoma eyes (12.7 ± 2.0 mm Hg) \((P = 0.175)\). All patients in the NTG group had been prescribed prostaglandin and a β blocker.

**Measurement the Amplitude of IOP Fluctuations**

We were able to successfully measure the 24-hour IOP in all 26 subjects. The wearing of the CLS resulted in no serious complications related to the CLS. Some subjects had minor complications: conjunctivitis, slight hyperemia, or peripheral corneal edema. These healed in a few days without any eye drops. An example of an IOP result is shown in Figure 1. The range of IOP fluctuations in the NTG group was significantly larger compared with the nonglaucoma group over the 24-hour observation \((P = 0.007)\), and during the diurnal periods \((P = 0.012)\), and during the nocturnal periods \((P = 0.0099)\) (Fig. 2).

We calculated a cutoff level to distinguish the glaucoma patients from the nonglaucoma subjects with receiver operating characteristic curve analysis. The cutoff level of IOP fluctuation was 442 mVeq (area under the curve, 0.857; sensitivity = 1.00; specificity = 0.571).

**Circadian IOP Patterns**

In our classification of the subjects into diurnal and nocturnal patterns, 11 to 12 (91.7%) subjects in the nonglaucoma group showed the nocturnal pattern. In the NTG group, 8 of 14 patients (57.1%) had the peak IOP in the nocturnal period (Fig. 3). None of the 26 subjects showed the unclassifiable pattern.

**Corneal Effects of the CLS**

To examine the effects of the CLS on the cornea, we analyzed corneal changes (Fig. 4). We measured the corneal curvature and CCT with the AS-OCT just before each of the subject’s contact lens with the CLS was inserted and just after it was removed. Table 2 shows the changes of corneal curvature, thickness, and IOP value. The mean steeper meridian was 44.65 ± 1.56 D before the contact lens insertion, and 45.23 ± 1.78 D after its removal, indicating slight but significantly progressing myopia \((P = 0.0091)\). The mean of the flatter meridian was 43.80 ± 1.59 D before the contact lens insertion and 43.98 ± 1.60 D after its removal.
The range of IOP values. A, Boxplots of the range of IOP values over the 24-hour recording period. The range of IOP was defined as the difference between maximum IOP and minimum IOP. B, The range of IOP values during the diurnal period of measurement. C, The range of IOP during the nocturnal period. The IOP fluctuations in the NTG group were significantly larger than those of the nonglaucoma group over the entire 24-hour measurements and during both the diurnal and nocturnal periods. IOP indicates intraocular pressure; NTG, normal tension glaucoma.

The peak times and range of IOP values. White dots indicate nonglaucoma subjects; black dots indicate NTG patients. The peak times of IOP fluctuation are plotted. Most of the white/nonglaucoma dots are included within the sleeping time. The size of the radius indicates the range of IOP fluctuation (mVeq). Black/NTG dots are located more outwardly compared with the white/nonglaucoma dots. IOP indicates intraocular pressure; NTG, normal tension glaucoma. Figure 3 can be viewed in color online at www.glaucomajournal.com.

The result of receiver operating characteristic curve analysis to distinguish glaucoma patients from nonglaucoma subjects. The cutoff level of 24-hour IOP fluctuation was 442 mVeq. Area under the curve, 0.857. Sensitivity = 1.00; Specificity = 0.571. Figure 4 can be viewed in color online at www.glaucomajournal.com.
TABLE 2. Change in the CCT, Corneal Curvature, and IOP Before and After the 24-Hour Measurement With Contact Lens Sensor

<table>
<thead>
<tr>
<th></th>
<th>Before Measurement</th>
<th>After Measurement</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCT (μm)</td>
<td>524.2 ± 32.7</td>
<td>528.5 ± 33.4</td>
<td>0.0022</td>
</tr>
<tr>
<td>Steeper meridian (D)</td>
<td>44.65 ± 1.56</td>
<td>45.23 ± 1.78</td>
<td>0.0091</td>
</tr>
<tr>
<td>Flatter meridian (D)</td>
<td>43.80 ± 1.59</td>
<td>43.98 ± 1.60</td>
<td>0.289</td>
</tr>
<tr>
<td>IOP (mm Hg)</td>
<td>12.1 ± 3.1</td>
<td>11.7 ± 2.4</td>
<td>0.387</td>
</tr>
</tbody>
</table>

CCT indicates central corneal thickness; IOP, intraocular pressure.

(P = 0.289 a nonsignificant difference). The mean CCT was 524.2 ± 32.7 μm before the contact lens insertion, and 528.5 ± 33.4 μm after its removal, which is significantly thicker before the insertion (P = 0.0022). The IOP value (measured with GAT) did not differ significantly between before and after the 24-hour measurement with the CLS in either group (P = 0.387).

DISCUSSION

We measured IOP fluctuations in 14 nonglaucoma subjects and 12 NTG patients with CLS, and showed the range of IOP fluctuations in the NTG group was significantly larger than that in the nonglaucoma group. In our study, the cutoff level of the range IOP fluctuation throughout 24 hours was 442 mVeq. Most of the nonglaucoma subjects had peak IOP fluctuations within the nocturnal periods.

In the Tajimi Study, a large Japanese epidemiology glaucoma investigation, the average IOP for eyes with primary open-angle glaucoma was 15.4 ± 2.8 mm Hg.11 It has been estimated that NTG is present in almost 70% of all glaucoma patients in Japan, and the lack of an effective treatment for glaucoma that does not lower the IOP is a significant problem. The Advanced Glaucoma Intervention Study (AGIS) showed in 2004 that the most important predictors for visual field progression are older age at the time of first glaucoma intervention, greater IOP fluctuation, higher mean IOP, and lower baseline AGIS visual field score.12 In AGIS, long-term IOP fluctuation was associated with visual field progression in patients with low mean IOP but not in patients with high mean IOP.13

The role of IOP fluctuation as a predictor of glaucoma progression beyond that of mean IOP reduction is controversial. Some reports said that IOP fluctuation was not related to glaucoma progression.14,15 The existing studies of IOP fluctuation can be divided into 2 short-term (throughout the day) studies and the long-term (several years) studies. It has been difficult to determine the significance of these variations due to the lack of standardization regarding the time between assessments, the methods of measurement, and the definition of fluctuation itself.

Using GAT, Kim et al16 reported that the 24-hour IOP fluctuation in NTG eyes was significantly larger than that in healthy eyes. In their methods, the IOP during the interval period between the IOP measurements was unknown. The burden of hospitalization and sleep disturbance should be avoided if possible when measuring IOP. The new methods of measurement of IOP fluctuation with a CLS can avoid these burdens and provide clearer assessment of circadian patterns of IOP.

We also expected to lessen the possibility of bias in measurement of IOP fluctuation by using the objective measurements provided by the CLS. Using a CLS methods, Agnifili et al17 reported that the IOP fluctuation of NTG eyes was larger than that in healthy eyes, which is in agreement with our present findings. They reported that both NTG and nonglaucoma subjects had peak IOP values in the nocturnal periods, and that the peak IOP time in the NTG patients was earlier than that in the nonglaucoma subjects, which was different from our data. Altintas et al18 contended that the significant IOP fluctuations in NTG may be an important factor in predicting the development of glaucoma. In the present study, we observed that the percentage of nonglaucoma subjects whose peak IOP fluctuation was within the nocturnal period was greater than that in the NTG group. Using GAT, other researchers reported that the percentage of NTG patients who showed the peak time of IOP while sleeping were 54.7% to 48.6%,19,20 which agrees with our results. It might be likely for glaucoma to show the peak IOP value with CLS within the diurnal periods.

Artifacts such as corneal swelling—a commonly observed phenomenon with the use of a CLS—may have affected our results. Hubanova et al21 reported that CCT and corneal curvature irregularities increased slightly but significantly more often in eyes that were measured with the Triggerfish CLS than in control eyes during overnight wear. Freiberg et al22 demonstrated that continuous IOP monitoring did not seem to be affected by differences in corneal thickness that occur during overnight CLS wear, although the CLS induced some corneal swelling in their study; however, the effect on the wearers did not result in a significant difference compared with the control eyes and did not seem to influence the CLS IOP profile. In our study, the CCT values after the removal of the CLS were significantly thicker than before the CLS worn (Table 2). Hypoxia with the resulting metabolic shift and corneal swelling might occur predominantly during extended contact lens wear in the nocturnal period, when the eye lids are closed.

It is well known that deepening of the upper eyelid sulcus (DUES) is one of the major side effects for glaucoma patients associated with topical prostaglandin therapy.23 There were 2 patients who were diagnosed with DUES. Their range of fluctuation IOP were not different from the others. It was difficult to say that DUES and the range of IOP fluctuation were relevant from our results.

Our study has several weaknesses. It was not possible to convert the recorded units of mVeq to units of mm Hg. The CLS recorded the relative IOP (not the absolute IOP) from the initial IOP. The relationship between the CLS device output and IOP as measured with a tonometer is unknown. This result might not lead directly to the conclusion that the IOP fluctuation of the NTG patients was larger than in the nonglaucoma subjects. In addition, we did not consider the effects of glaucoma medications, posture changes, and artifacts. In this study, IOP fluctuations of the NTG patients were not measured with CLS in the untreated condition. Holló et al24 reported that no difference was seen between the sitting-period and the supine-period CLS values.

In relation to glaucoma medication, it was reported that prostaglandin treatment in glaucoma patients could be accompanied by smaller IOP fluctuation than that observed...
without medication. However, when >2 glaucoma medications were prescribed for all patients with NTG in the previous study, the IOP fluctuation was larger than that of the nonglaucoma group who did not use any glaucoma medication. The true IOP fluctuation of the NTG patient might be bigger. Pajic et al\textsuperscript{25} compared IOP fluctuations between treated and untreated NTG patients with CLS. They reported that the range of IOP fluctuations of treated NTG patients was smaller than that of untreated patients in the nocturnal periods. In another study, Hollo and colleagues reported that a CLS technique cannot be clinically used to monitor the IOP decrease induced by topical medication in glaucoma.\textsuperscript{23}

Leonardi et al\textsuperscript{10} demonstrated that the IOP and the output by CLS were directly proportional. Mansouri et al\textsuperscript{27} reported that the CLS outputs agreed with pneumotonometer measurements of the contralateral eye. Liu et al\textsuperscript{28} reported that the peak IOP time with CLS and with the pneumotonometer measurements of the contralateral eye were similar, but variations of 24-hour data in the paired eyes were not correlated. The evaluation of CLS methods clearly merits further study. However, our present findings agree with those of previous studies using GAT in relation to IOP fluctuation. In light of the existing data, the large amplitude might be due to large IOP fluctuation.

Greater IOP fluctuation may be a contributory factor in NTG. In this regard, treatment for glaucoma is needed not only to reduce a temporary IOP, but also to lessen IOP fluctuation. IOP measurement with a CLS might become an essential test for glaucoma patients. Even though there are some limitations regarding the use of a CLS, the continuous measurement of peak IOP value and habitual IOP fluctuation can provide useful information. Investigations using 24-hour continuous IOP measurement with a CLS may help distinguish NTG patients from nonglaucoma subjects.

REFERENCES


