Continuous 24-Hour Monitoring of Intraocular Pressure Patterns With a Contact Lens Sensor

Safety, Tolerability, and Reproducibility in Patients With Glaucoma

Kaweh Mansouri, MD, MPH; Felipe A. Medeiros, MD, PhD; Ali Tafreshi, BS; Robert N. Weinreb, MD

Objective: To examine the safety, tolerability, and reproducibility of intraocular pressure (IOP) patterns during repeated continuous 24-hour IOP monitoring with a contact lens sensor.

Methods: Forty patients suspected of having glaucoma (n=21) or with established glaucoma (n=19) were studied. Patients participated in two 24-hour IOP monitoring sessions (S1 and S2) at a 1-week interval (SENSIMED Triggerfish CLS; Sensimed AG). Patients pursued daily activities, and sleep behavior was not controlled. Incidence of adverse events and tolerability (visual analog scale score) were assessed. Reproducibility of signal patterns was assessed using Pearson correlations.

Results: The mean (SD) age of the patients was 55.5 (15.7) years, and 60% were male. Main adverse events were blurred vision (82%), conjunctival hyperemia (80%), and superficial punctate keratitis (15%). The mean (SD) visual analog scale score was 27.2(18.5) mm in S1 and 23.8(18.7) mm in S2 (P=.22). Overall correlation between the 2 sessions was 0.59 (0.51 for no glaucoma medication and 0.63 for glaucoma medication) (P = .12). Mean (SD) positive linear slopes of the sensor signal from wake to 2 hours into sleep were detected in both sessions for the no glaucoma medication group (S1: 0.40[0.34], P < .001; S2: 0.33[0.30], P < .01) but not for the glaucoma medication group (S1: 0.24[0.60], P = .06; S2: 0.40[0.40], P < .001).

Conclusions: Repeated use of the contact lens sensor demonstrated good safety and tolerability. The recorded IOP patterns showed fair to good reproducibility, suggesting that data from continuous 24-hour IOP monitoring may be useful in the management of patients with glaucoma.

Trial Registration: clinicaltrials.gov Identifier: NCT01319617


Elevated intraocular pressure (IOP) is a major risk factor for glaucoma.1 Goldmann applanation tonometry (GAT) is considered the criterion standard for measuring IOP,2 but its measurements are influenced by central corneal thickness (CCT), corneal biomechanical properties, and scleral rigidity.3 The most significant shortcoming of GAT, however, is the static nature of its measurements. Yet, IOP is a dynamic parameter with distinct circadian rhythms that vary among individuals, and single IOP measurements may fail to reflect the true range of an individual’s IOP.5,6

Currently, the most common methods for studying glaucoma patients’ 24-hour IOP rhythm are through a diurnal tension curve or while hospitalized in a sleep laboratory. The former only provides daytime IOP values, whereas the latter is expensive and requires awakening of patients during the nocturnal/sleep period, potentially introducing stress-related artifacts.7 Most important, both methods do not provide IOP measurements during undisturbed sleep. Studies performed under the controlled environment of sleep laboratories have shown that the IOP of most glaucoma patients is at its highest during the nocturnal/sleep period with the patient in the supine position.6,8

Recently, a contact lens sensor (CLS; SENSIMED Triggerfish, Sensimed AG) was developed to monitor IOP continuously for 24 hours in an ambulatory setting.9-11 Despite some initial experience,12,13 it is not known how glaucoma patients would tolerate this CLS for repeated 24-hour periods and whether results from one monitoring session will be reproducible in the short term. This study investigates the safety and tolerability of CLS in patients with suspected or established glaucoma and evaluates the reproducibility of 24-hour IOP patterns during repeated use.
METHODS

The University of California at San Diego Human Research Protections Program approved the study, and informed consent was obtained from all participants.

STUDY POPULATION

Forty eyes of 40 patients were studied in 2 study sessions (S1 and S2) each 7 ± 1 days apart. On day 1, patients underwent comprehensive ophthalmologic examination and standard automated perimetry with the 24-2 Swedish Interactive Threshold Algorithm (Carl Zeiss Meditec, Inc). Patients were also asked to report their activities in a standardized logbook every 30 minutes. They were then discharged and could pursue their routine daily activities. After 24 hours (day 2), patients returned, the CLS was removed, and an ophthalmologic examination was performed. Any change from baseline in relevant ocular parameters, as assessed by the investigator or the patient, was defined as an adverse event (AE). Before removal of the CLS, patients were asked to score their subjective comfort level using the visual analog scale (VAS), with scores ranging from 0 (no discomfort) to 100 (very severe discomfort), the number corresponding to the distance in millimeters of the participant’s mark on the VAS line from the left end.14 The same procedures were repeated a week later (S2).

Individuals were enrolled in the study if they met the following criteria: age between 18 and 80 years, best-corrected visual acuity of 20/80 or greater in the study eye, spherical refraction between −5 and 3 diopters (D), cylinder correction of 2 D or less, and open angles on gonioscopy. Individuals with any of the following were excluded: previous glaucoma surgery or any intraocular surgery 3 months before study inclusion, known intolerance to silicone, contraindications for contact lens wear, and severe dry eye disease, keratoconus, or other corneal abnormality. When both eyes of an individual were eligible, 1 eye was chosen at the discretion of the investigators. To be classified as glaucomatous, eyes had to have at least 2 consecutive, reliable, and repeatable standard automated perimetry examinations with either a pattern standard deviation outside the 95% confidence limits or a glaucoma hemifield test result outside the 99% confidence limits. Patients suspected of having glaucoma were defined as those with eyes with abnormal-appearing optic discs by masked stereophotograph assessment without repeatable abnormal standard automated perimetry results. Patients suspected of having glaucoma also included those with eyes with an IOP greater than 22 mm Hg but with healthy-appearing optic discs by masked stereophotograph assessment without repeatable abnormal standard automated perimetry results.

INSTRUMENTATION

The CLS consists of a highly oxygen-permeable soft contact lens (SCL), whose key elements are 2 sensing-resistive strain gauges that are capable of recording circumferential changes in the area of the corneoscleral junction. It is approved for clinical use in Europe (CE mark) but only admitted for investigational use in the United States. The device is based on a novel approach to IOP monitoring in which changes in corneal curvature and circumference are assumed to correspond to changes in IOP.9,13 A microprocessor embedded in the contact lens sends an output signal proportional to the contact lens strain gauge. Wireless power and data transfer are achieved using a paired periorbital antenna from where a cable is connected to a portable recorder. The portable unit is worn around the patient’s waist. Silicone was chosen for the contact lens material because of its high oxygen permeability and minimal water absorption (0.2% in weight). The disposable contact lens exists in 3 different base curves (8.4 mm [steep], 8.7 mm [medium], and 9.0 mm [flat]), with a diameter of 14.1 mm and a thickness of 585 µm at the center and 260 µm at the border. According to the manufacturer’s user manual, individuals with a central corneal radius in the flatter meridian between 7.54 and 8.44 mm were fitted with a medium CLS, those with lower values with a steep CLS, and those with higher values with a flat CLS. Thirty-four of 40 individuals (92%) received a medium CLS. The device can record IOP fluctuations for up to 24 hours and remains active during undisturbed sleep. Three hundred data points are acquired during a 30-second measurement period, repeated every 5 minutes. The output of the sensor is expressed in arbitrary units.

STATISTICAL ANALYSIS

The GAT IOP and CCT measurements taken before and after IOP monitoring with the CLS were compared using a paired t test for both sessions. Primary safety end points included the incidence of AEs and the VAS scores at each session. The secondary end point was the reproducibility of circadian IOP patterns between the 2 sessions. To assess the degree with which individual patient patterns were similar during the 2 sessions, Pearson correlation was computed between CLS outputs in both sessions for each patient separately. Between-patient similarity was assessed by computing pairwise correlations of CLS outputs across sessions between each patient and all others and, for each patient, averaging the pairwise correlations obtained with all other patients. Within-patient–across-session relationships were obtained by correlating parallel recording time points, using each of the 5-minute recordings. Thus, patients’ recordings every 5 minutes were “lined up” by time across the 2 sessions and the paired recordings correlated by Pearson correlations.

\[ r < 0.4 \text{ was considered poor correlation, } r = 0.4 \text{ to } 0.75 \text{ was considered fair to good correlation, and } r > 0.75 \text{ was considered excellent correlation.} \]

To assess the degree of change in IOP output over time, a regression was fit to each patient’s data from 1 hour before going to sleep to 2 hours into sleep and from 1 hour before going to sleep to the end of the sleep period. Sleep times were derived from the patients’ diary entries. The regression allowed for linear trends to be modeled. The linear slopes were tested for significance using a paired t test.

All hypothesis testing was 2-sided at a 2-sided \( \alpha = 0.05 \). All analyses were conducted using SAS statistical software, version 9.2 or higher (SAS Institute, Inc).

RESULTS

DEMOGRAPHICS

Forty eyes of 40 patients were included in the study (55% were right eyes). The mean (SD) age of patients was 55.5 (15.7) years (range, 20–77 years). Sixty percent of patients (24 of 40) were male. Twenty-nine patients (72%) identified themselves as white, 5 (12%) as Asian, 3 (8%) as African American, and 3 (8%) as Latino. There were 21 patients suspected of having glaucoma (52%) and 19 patients (48%) with primary open-angle glaucoma. Twenty-seven eyes (68%) were treated with glaucoma drops. Table 1 provides an overview of the clinical parameters at baseline. Table 2 lists the changes in ocular parameters before and after CLS wear.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Overview of the Clinical Parameters at Baseline</th>
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<tbody>
<tr>
<td>Age</td>
<td>55.5 (15.7) years (range, 20–77 years)</td>
</tr>
<tr>
<td>Gender</td>
<td>60% male, 40% female</td>
</tr>
<tr>
<td>Race</td>
<td>29% white, 12% Asian, 8% African American, 8% Latino</td>
</tr>
<tr>
<td>Nearsightedness</td>
<td>52% glaucoma, 48% primary open-angle glaucoma</td>
</tr>
</tbody>
</table>

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SAFETY

The study population for the safety analysis included all 40 patients from both sessions. The mean (SD) length of use of the CLS was 24.0 (0.5) hours in S1 and 24.0 (0.3) hours in S2. The investigators attributed most of the AEs (149 of 151 AEs in 38 of 40 patients) to the device. Two cases of mild headache constituted non–device-related AEs. Thirty-eight patients experienced 149 AEs: two 24-hour IOP monitoring sessions was found in 4 patients (10%) in S1 and 3 patients (8%) in S2 with a mean (SD) VAS score of 69.0 (9.3) mm in S1 and 76.3 (2.5) mm in S2 (P = .25). A positive correlation was found between the VAS score and the presence of AEs (r = 0.30; P = .008) and a negative correlation between VAS score and age (r = −0.14; P = .33).

REPRODUCIBILITY OF IOP PATTERNS

Complete 24-hour recordings were available from 37 patients in S1 and 39 patients in S2. The population for the reproducibility analysis included 36 patients with complete data from both sessions. For the 4 patients with incomplete recordings, a mean (SD) of 11.6 (3.1) hours of data were available. Reasons for incomplete data recording were battery insufficiency (n = 2), disconnection of device by the patient (n = 1), and unknown (n = 1).

To study circadian IOP patterns, Pearson correlations were used to assess the association of IOP changes between pairs of intervals across sessions. With all patients considered together, the correlation between the two 24-hour IOP monitoring sessions was r = 0.59. When stratified by use of antihypertensive glaucoma eye-drops, the 2 groups had no statistically significant differences (r = 0.51 for no glaucoma medication and r = 0.63 for glaucoma medication) (P = .12). These values indicate fair to good agreement.6 The Figure, A-D, provides examples of repeat 24-hour IOP monitoring results for 4 patients with different degrees of correlation.

To study the CLS signal change from the wake/sitting to the sleep/supine state, linear regressions were fitted to the transition from the wake to the sleep period. On average, mean (SD) positive linear slopes from 1 hour before sleep to 2 hours into sleep in S1 (0.30 [0.52], P = .002) and in S2 (0.38 [0.37], P < .001) were detected. Pearson correlation between the 2 sessions was r = 0.71. A statistically significant mean (SD) increase was found in both sessions for the no glaucoma medication group (S1: 0.40 [0.34], P < .001; S2: 0.33 [0.30], P < .01) but not for the glaucoma medication group (S1: 0.24 [0.60], P = .06; S2: 0.40 [0.40], P < .001). Twelve patients (33%) did not have a statistically significant increase in the slope in both sessions, with all but 1 of these patients using glaucoma eye-drops. Among these, 2 patients (6%) had a statistically significant negative slope in 1 session and 3 patients (8%) in both sessions.

TOLERABILITY

Data were available from all patients and both sessions. On average, patients reported a mean (SD) VAS score of 27.2 (18.5) mm in S1 and 23.8 (18.7) mm in S2 (P = .22), indicating moderate to good tolerability.14 The change between sessions was not statistically (P = .22) or clinically significant.14 Overall, the mean (SD) VAS score was 23.1 (16.2) mm and 28.1 (20.8) mm in patients with suspected and established glaucoma, respectively (P = .34). Poor tolerability (defined as a VAS score > 54 mm)14 was found in 4 patients (10%) in S1 and 3 patients (8%) in S2 with a mean (SD) VAS score of 69.0 (9.3) mm in S1 and 76.3 (2.5) mm in S2 (P = .25). A positive correlation was found between the VAS score and the presence of AEs (r = 0.30; P = .008) and a negative correlation between VAS score and age (r = −0.14; P = .33). No statistically significant correlations were found between VAS score and presence of conjunctival hyperemia (−0.10; P = .36), sex (r = 0.08; P = .496), glaucoma status (r = −0.14; P = .23), or use of glaucoma eyedrops (r = 0.11; P = .33).

COMMENT

The current study demonstrates that CLS is a safe and well-tolerated device for repeated use in glaucoma patients or those suspected of having the disease. Being integrated in an SCL, this device may be subject to AEs similar to those known to occur with any SCL used for vision correction. The electronic circuitry and other integrated elements of the CLS can be a potential source of

Table 1. Clinical Characteristics of the Study Patients at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
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<tbody>
<tr>
<td>BCVA</td>
<td>0.9 (0.2)</td>
</tr>
<tr>
<td>Objective refraction</td>
<td></td>
</tr>
<tr>
<td>Sphere, D</td>
<td>−2.2 (2.7)</td>
</tr>
<tr>
<td>Cylinder, D</td>
<td>0.6 (0.7)</td>
</tr>
<tr>
<td>Axis, °</td>
<td>57.9 (78.4)</td>
</tr>
<tr>
<td>TUT, s</td>
<td>12 (2.8)</td>
</tr>
<tr>
<td>CCT, μm</td>
<td>568.1 (62.5)</td>
</tr>
<tr>
<td>Horizontal CCR, D</td>
<td>43.5 (1.7)</td>
</tr>
<tr>
<td>Horizontal CCR axis, °</td>
<td>79.9 (72.1)</td>
</tr>
<tr>
<td>Vertical CCR, D</td>
<td>43.4 (1.5)</td>
</tr>
<tr>
<td>Vertical CCR axis, °</td>
<td>85.9 (33.6)</td>
</tr>
<tr>
<td>Axial length, mm</td>
<td>24.5 (1.2)</td>
</tr>
<tr>
<td>Visual field mean deviation, dB</td>
<td>−1.5 (2.6)</td>
</tr>
<tr>
<td>Visual field PST, dB</td>
<td>2.6 (1.9)</td>
</tr>
<tr>
<td>Vertical cup to disc ratio</td>
<td>0.7 (0.1)</td>
</tr>
<tr>
<td>Average thickness of RNFL, μm</td>
<td>79.9 (10.6)</td>
</tr>
<tr>
<td>Glaucoma eyedrops, No.</td>
<td>1.2 (1.2)</td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best-corrected visual acuity; CCR, central corneal curvature; CCT, central corneal thickness; D, diopters; PST, pattern standard deviation; RNFL, retinal nerve fiber layer; TUT, tear break-up time.
additional complications. To our best knowledge, the current study is the first to investigate the reproducibility of IOP patterns during repeated 24-hour periods in patients with established and suspected glaucoma.

Mansouri and Shaarawy described the initial clinical experience with the CLS in glaucoma patients and reported 1 case of corneal erosion (7%) and 4 cases of superficial punctate keratitis (27%). These findings were later confirmed by De Smedt et al in 10 healthy individuals. In their cohort, 3 individuals (30%) had corneal microerosions that were treated prophylactically with antibiotic eyedrops. At the time of these studies, the availability of only 1 base curve may have produced suboptimal fit of the CLS. The current study was designed to evaluate the safety and tolerability of the second-generation CLS for repeated short-term use. The only AEs of note were blurred vision and conjunctival hyperemia. The AE of blurred vision is explained by (1) refractive power of the CLS itself; (2) orthokeratologic effect of the CLS as a result of its (intended) tight fit, which is demonstrated by the change in corneal curvatures and a mean reduction in best-corrected visual acuity by 0.17 (decimal scale) after CLS removal (Table 2); and (3) potential disturbance of peripheral vision by CLS elements. Therefore, patients were advised to drive carefully or refrain from driving if possible. On the basis of patient reports, vision returned to baseline levels within 24 hours of CLS removal.

Although the incidence of conjunctival hyperemia was high (80%), its intensity was graded as mild in 94% of patients. In all patients, hyperemia was transient and disappeared shortly after removal of the CLS, although in 1 patient, it lasted up to 3 days. Hyperemia itself was not associated with other safety findings or discomfort. The incidence of AEs is consistent with previous reports on complications of SCL use. Brautaset et al studied 330 silicone-hydrogel contact lens users and found conjunctival and corneal staining in 32.5% and 19.5% of subjects, respectively. The proportion of patients who developed corneal staining in the current study (15%) is in the lower range of studies with modern SCLs. Furthermore, because no association has been found between corneal staining and corneal infection, corneal staining is considered a minor AE. The current study was conducted on glaucoma patients and those suspected of having glaucoma and differs from other populations who were largely healthy volunteers. Because the CLS is embedded in an SCL with an oxygen transmissibility (Dk/t) of $120 \times 10^{-9}$ Fatt units, a value that was shown not to cause stromal hypoxia, we believe that factors other than hypoxia, such as the tight fit of the CLS, may have been more contributory. Ocular surface disease is a common finding in pharmacologically treated glaucoma patients and may have contributed to increased conjunctival inflammatory reaction in these patients. Patients were informed of this complication in advance and provided with artificial tears, which may explain the absence of a correlation between VAS score and the presence of conjunctival hyperemia. The absence of corneal erosions and corneal infiltrative events, seen in previous reports, may also be explained by improved fitting of the CLS through the availability of 3 base curves.

With any diagnostic technology, the assessment of measurement reproducibility is necessary to distinguish measurement variability from physiologic changes. Previously, Wilensky et al assessed reproducibility of IOP patterns by collecting 5 home tonometry measurements during 4 to 8 consecutive days. Subjective assessment of curve shapes revealed that only 28% of patients with ocular hypertension and 34% of patients with open-angle glaucoma had reproducible curve shapes. Realini et al studied the repeatability of diurnal GAT measurements in healthy volunteers and treated glaucoma patients. They reported intraclass correlation coefficients ranging from 0.45 to 0.83.
to 0.71 for IOP values at each time point between the 2 visits. The fact that IOP measurements were assessed during 12 hours and not the entire 24-hour period may have limited the conclusions of their investigation.

To our knowledge, the current study is the first to assess the short-term reproducibility of IOP patterns throughout the full 24-hour cycle, including undisturbed sleep made possible through the availability of the CLS for clinical use. The current generation of this technology does not display the output signal in millimeters of mercury but in arbitrary units that are proportional to the electric signal generated by the contact lens–embedded strain gauge. This limitation precludes the use of intraclass correlation coefficients for the statistical reproducibility analysis. Instead, we used the Pearson correlation, which does not directly measure reproducibility but an association of measurements, to compare changes in signal values between pairs of intervals across sessions. The overall r of 0.59 for the entire 24-hour period indicates fair to good agreement.

It has been shown that IOP increases when individuals go from sitting/wake to supine/sleep. To study this change, linear slopes were constructed from 1 hour before sleep to 2 hours into sleep. The slopes were positive in both sessions for untreated glaucoma patients but not for the treated patients. A third of patients did not show a significant positive slope when going from the wake to the sleep state. This lack of a clear pattern is similar to a recent report of Asian patients with a diagnosis of normal-tension glaucoma but higher than reported in a white population with normal-tension glaucoma. Patients in this study were advised to follow their daily routine and were not controlled for sleep times, physical activity, and environmental factors. It is possible that reproducibility of IOP patterns may have been higher in a controlled environment.

The technology of the CLS can be subject to artifacts. Because the output signal of the CLS depends on changes occurring at the corneoscleral junction, non–IOP-related changes in corneal shape and thickness may potentially affect the device output. Normal 24-hour changes in biomechanical properties of the cornea were not found to have a significant effect on circadian GAT IOP in young healthy individuals but may play a role in older glaucoma patients. Normal corneal swelling may be emphasized by the SCL acting as an additional barrier to oxygen delivery. In the current study, a small but significant change in CCT before and after CLS monitoring was found in 1 of 2 sessions. Other potential artifacts related to corneal biomechanical properties should be studied. For pragmatic purposes, we used the term continuous to describe
the near-continuous character of 24-hour monitoring with the CLS because the measurements are taken at 10 Hz for 30 seconds every 5 minutes and do not capture high-frequency IOP fluctuations between those data capture intervals. Therefore, IOP changes due to blinks, saccades, eye rubbing, and other phenomena that occur on a shorter timescale would only be captured intermittently by this system.

This study reveals that CLS provides a safe and well-tolerated approach to 24-hour IOP monitoring in glaucoma patients. The 24-hour IOP patterns seem to be fairly reproducible when repeated in the short term. The availability of continuous 24-hour IOP monitoring holds the promise to improve glaucoma care.

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Correspondence: Robert N. Weinreb, MD, Hamilton Glaucoma Center, Department of Ophthalmology, University of California, San Diego, 9500 Gilman Dr, La Jolla, CA 92039-0946 (rweinreb@ucsd.edu).

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