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Enregistrement des fluctuations de la pression intraoculaire sur 24 heures par une lentille de contact intégrant un capteur: tolérance et résultats chez 10 sujets sains

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THESE

préparée sous la direction du Docteur Corinne Schnyder PD, MER

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par

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Enregistrement des fluctuations de la pression intraoculaire sur 24 heures par une lentille de contact intégrant un capteur: tolérance et résultats chez 10 sujets sains

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de la Faculté de Biologie et de Médecine

Madame le Professeur Stephanie Clarke
Directrice de l'Ecole doctorale

Rapport de synthèse

Contexte et objectifs:

Le glaucome est une neuropathie optique progressive caractérisée par une excavation du disque optique accompagnée par une perte du champ visuel et de l'acuité visuelle. L'un des facteurs de risque bien connus du glaucome est une pression intraoculaire (PIO) élevée, ainsi qu' une variation nycthémérale importante de la PIO. Or, il est difficile de bien documenter la fluctuation de la PIO d' un patient, par ce que les mesures obtenues dans un cabinet médical ne reflètent pas les valeurs de la PIO au cours de la journée ni ses fluctuations. La compagnie Sensimed a développé une nouvelle méthode de mesure pour la PIO, basée sur l'utilisation d' une lentille de contact en silicone souple à usage unique intégrant un capteur (SENSIMED Triggerfish®) permettant de mesurer les déformations minimes de la cornée lors des changements de PIO, pour en déduire ainsi les changements de PIO. Des résultats in vitro sur des yeux de porc ont permis de démontrer l'excellente corrélation entre les fluctuations de PIO induites dans ces yeux et des changements de courbure cornéenne mesurés au limbe. Les premières expériences in vivo ont confirmé la validité de l'enregistrement d' un changement de PIO artificiellement induit par un scuba-masque pendant 10 minutes. L'objectif de notre étude était d' évaluer chez 10 volontaires la précision et la stabilité de la mesure du signal fourni par le capteur, ainsi que le confort du volontaire avec ce capteur pendant 24 heures.

Matériel et méthode:

Après un examen ophtalmologique complet un capteur oculaire télémétrique était posé sur l'œil du volontaire, ainsi qu' une antenne de transmission télémétrique pour l'enregistrement de la PIO, collée sur la peau périorbitaire. Un dispositif portable externe, connecté à l'antenne périorbitaire par un câble de données, enregistrait les données durant 24 heures. Un contrôle ophtalmologique était effectué pendant le port du capteur après 5 et 30 minutes, 4, 7 et 24 heures. Ce contrôle comportait la mesure de l'acuité visuelle optimalement corrigée, un examen à la lampe à fente pour évaluer le comportement du capteur, sa mobilité spontanée et lors qu'il est poussé vers le haut (push-up test). Le volontaire notait par un score de 1 à 10 son confort par rapport au capteur oculaire. Après 24 heures les données de l'enregistrement étaient téléchargées à travers un système Bluetooth vers l'ordinateur et l'examen ophtalmologique complet était répété.

Résultats :

Le score de confort par rapport au capteur oculaire noté par les volontaires était haut et ne changeait pas significativement au cours de 24 heures. La mobilité du capteur oculaire était limitée durant les contrôles. L'acuité visuelle optimalement corrigée était réduite significativement pendant le port du capteur et immédiatement après son enlèvement. Trois volontaires développaient une érosion cornéenne mineure transitoire. Chez tous les volontaires sauf un, les données de l'enregistrement ont été capturés montrant un signal télémétrique utile avec des pulsations oculaires visibles.

Conclusions:

Cette étude produisait des résultats encourageants sur la précision et la stabilité de la mesure du signal fourni par le capteur, ainsi que le confort du volontaire avec ce capteur pendant 24 heures. Afin d'améliorer le confort, la précision et l'interprétation du signal télémétrique, on a besoin de futures études utilisant des capteur oculaires télémétriques de différent courbature sur une plus grande nombre de participants.

Le travail de thèse : article accepté pour publication dans « Journal of Glaucoma »

24 hour-intraocular pressure fluctuation monitoring using an ocular telemetry Sensor: tolerability and functionality in healthy subjects.

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Abstract

Purpose: to evaluate the tolerability, comfort and precision of the signal transmission of an ocular Sensor used for 24-hour intraocular pressure fluctuation monitoring in humans.

Patients and methods: In this uncontrolled open trial involving 10 healthy volunteers an 8.7 mm radius prototype ocular telemetry Sensor (SENSIMED Triggerfish®, Lausanne, Switzerland) and an orbital bandage containing a loop antenna were applied and connected to a portable recorder after full eye examination. Best corrected visual acuity and position, surface wetting ability and mobility of the Sensor were assessed after 5 and 30 minutes, 4, 12 and 24 hours. Subjective wearing comfort was scored and activities documented in a logbook. After Sensor removal a full eye examination was repeated and the recorded signal analyzed.

Results: The comfort score was high and did not fluctuate significantly over time. The mobility of the Sensor was limited across follow-up visits and its surface wetting ability remained good. Best corrected visual acuity was significantly reduced during Sensor wear and immediately after its removal (from 1.07 before, to 0.85 after, P-

value 0.008). Three subjects developed a mild, transient corneal abrasion. In all but one participant we obtained usable data of a telemetric signal recording with sufficient sensitivity to depict ocular pulsation.

Conclusions: This 24-hour- trial has encouraging results on the tolerability and functionality of the ocular telemetric Sensor for intraocular pressure fluctuation monitoring. Further studies with different Sensor radii conducted on a larger study population are needed to improve comfort, precision and interpretation of the telemetric signal.

Introduction

Glaucoma is a chronic optic neuropathy characterized by the excavation of the optic disc due to the atrophy of the retinal ganglion cells. A progression of such atrophy leads to further reduction of the visual field and eventually to the loss of sight at the end-stage of the disease. Glaucoma is the second leading cause of blindness worldwide [1]. Large diurnal intraocular pressure (IOP) fluctuation is an established risk factor for the development and progression of glaucoma [2-5]. It has been shown that analyzing the IOP curves allows a more accurate detection of the IOP fluctuations and peak values, which, in 52 to 69 % of patients, occur outside office hours [6-8]. With current available tonometers (Goldmann, I-care, Tonopen) such IOP curves are established by repeated IOP measurements e.g. every 4 hours over a period of up to 24 hours. However, 24-hour IOP measurements on an in-patient basis with current methods are unpractical and therefore not appropriate as a routine clinical tool, while self-monitoring requires a significant amount of manual dexterity for some devices and cannot cover the nocturnal period [9]. Continuous IOP monitoring

is therefore an unmet need following diagnosis of the disease [10, 11]. While not universally confirmed [12], two separate groups [13, 14] demonstrated a correlation between IOP and corneal curvature in human eyes , in which an IOP change of 1 mm Hg causes a change of central corneal radius of curvature of approximately 3 µm. Accurate detection of these changes using the ocular telemetry Sensor (SENSIMED Triggerfish®, Lausanne, Switzerland) has already been shown *ex vivo* [15]. During an in vitro study using a Sensor with an embedded micro-fabricated strain gauge, Leonardi et al demonstrated on porcine eyes a very good correlation between the intraocular pressure variations and the changes in the corneal curvature measured at the corneoscleral junction, where it is believed IOP changes induce maximum corneal deformation [16]. In a second experiment the same authors confirmed these results using a wireless Sensor on enucleated porcine eyes [17]. They were able to significantly reduce the noise so as to be able to detect an artificially induced IOP change over a 10-minute interval in 4 human volunteers [18]. This device had the potential to monitor the IOP over a prolonged period using a minimally invasive technique, regardless of the position of the patient and his activities, thus opening up new perspectives for the management of glaucoma. The aims of our study were to evaluate the tolerability, comfort and precision of signal transmission of the Sensor during a continuous IOP recording in healthy volunteers over a 24-hour period. A preliminary analysis of the resulting circadian IOP curves was also performed.

Methods

In this prospective uncontrolled open trial, 10 healthy volunteers were recruited fulfilling the inclusion criteria of being aged 21 years or over, not being pregnant, not

suffering from glaucoma or any ocular surface disorder and not having undergone ocular surgery in the last 3 months. The volunteers underwent a full eye examination including evaluation of the best corrected visual acuity, slit lamp examination, Goldmann applanation tonometry (GAT), pachymetry (Ocuscan®, Alcon laboratories, USA), automatic keratometry, measurement of the pupil and horizontal corneal diameters (Nidek RKT-7700®, Japan), gonioscopy and fundoscopy. The Sensor used in this study was made of silicone with oxygen plasma-treated surface to make it hydrophilic and contained a thin micro-fabricated platinum-titanium strain gauge as sensor and a gold loop antenna, which was interconnected to a telemetric microprocessor for wireless power and data transfer to a loop antenna located in an orbital bandage (figure 1). The diameter and radius of the Sensor used in this study were respectively 14.4 mm and 8.7 mm and its thickness was 100 µm at the border and 600 µm at the centre. The microfabricated strain gauge was centred on a circumference of 11.5 mm diameter, which is the average of the corneoscleral junction position. On one eye, chosen at the discretion of the investigators, the Sensor was placed, the orbital bandage was applied around the orbit and connected to a portable recorder worn around the volunteer's waist (figure 2). The volunteers were seen by the investigators at 5 and 30 minutes, 4 hours, 12 hours and 24 hours thereafter. Parameters such as the conjunctival injection, the position and surface wetting ability of the Sensor and its mobility on blinking and during push-up maneuver were assessed on the slit lamp. The anterior surface wetting ability of the Sensor was also assessed based on the reflection of the Javal keratometer mires and best corrected visual acuity was taken. Subjective volunteer comfort was scored from zero to 10, zero being intolerable and 10 perfect. During this 24-hour period the volunteers were requested to document their activities in a logbook in order to be able to

correlate such activities to the recorded corneal curvature changes. Twenty-four hours later the Sensor was removed and the full eye examination repeated. Any adverse events were recorded and treatment offered if necessary. At the end of the recording, data from the portable recorder were transferred via a bluetooth link to a computer containing the software for analysis of the signal. The output of the Sensor was expressed in arbitrary units (a.u.). This study was in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of the University of Lausanne and Swissmedic. A written informed consent was obtained from all volunteers. Wilcoxon non-parametric signed rank test was used for statistical analysis of the differences in parameters over time (SAS stats program) and a significance level was set on P-value less than 0.05. The minimal detectable difference (MDD) for each of the parameters of interest were calculated with 80% power, taking into account the sample size (N = 10) and the observed standard deviation of the parameter's difference from its value at baseline.

Results

Table 1 shows the baseline characteristics of the study subjects. There was an equal number of men and women participating. Three participants were co-workers. All Sensors were placed and removed in the mornings, except one. Slit lamp examination and fundoscopy findings were normal except for one subject with some lens opacities and one with a narrow angle on gonioscopy. No subject had glaucomatous discs and no topical or systemic anti-glaucoma medication was used. Three subjects were regular optical correcting contact lens wearers. The evolution in the subjective refractive error (spherical and cylindrical equivalent) and the best

corrected visual acuity is shown in table 2, and were expressed as the mean, the standard deviation (SD) and the range. The P-value represents the significance for the difference with the visit prior to Sensor wear. After removal of the Sensor a significant but transient myopisation of the subjects occurred (P-value 0.018), normalizing within 48 hours. Best corrected visual acuity was significantly reduced during the Sensor wear at each visit and this reduction remained statistically significant immediately after removal of the Sensor (from 1.07 before, to 0.85 after, P-value 0.008). However, this was clinically significant for only one participant and did not persist beyond 48 hours after removal. Similar changes before and after Sensor-wear were found among the subgroup of contact lens wearers for subjective spherical correction (P-value 0.018) and BCVA (P-value 0.008). After removal of the Sensor at the end of the 24-hour-wear vertical corneal radius was statistically (P-value 0.025) smaller (mean 7.41 mm, SD 0.21, range 7.01-7.63 mm) than before the placing (mean 7.53 mm, SD 0.21, range 7.18-7.88 mm). This difference remained significant while considering the 9 morning Sensor placements (P-value 0.05) and the contact lens wearers (P-value 0.025) separately. For the horizontal radius this difference before Sensor wear (mean 7.65 mm, SD 0.27, range 7.19-8.22 mm) and after Sensor-removal (mean 7.59 mm, SD 0.33, range 7.2-8.3 mm) was not significant (MDD 0.06 mm, P-value 0.201). No statistically significant difference (MDD 15.38 µm, P-value 0.695) was noticed in corneal thickness before (mean 549.4 µm, SD 33.91, range 517-610 µm) and after the Sensor wear (mean 549.1 µm, SD 43.52, range 489-613 µm), nor was there a significant difference in IOP (MDD 2.58 mmHg, P-value 0.266) measured by GAT before (mean 14.7 mm Hg, SD 3.33, range 10-20 mm Hg) and after (mean 13.7 mm Hg, SD 2.41, range 10-18 mm Hg). Figure 3 represents the mean comfort score across visits with its 95%-confidence interval.

Applying a repeated measures model to the data, the comfort score remained high (from 8.35 to 7.35 out of 10) and did not differ significantly over time from the baseline visit with Sensor at 5 minutes (MDD 1.84, P-value 0.16). Regular contact lens wear and being a co-worker did not influence this difference significantly (P-values 0.73 and 0.723 respectively). The change in telemetric microprocessor chip position expressed in clock hours compared to the baseline examination at 5 minutes after Sensor insertion was not statistically significant for any of the visits (P-value 1 at 30 min and 4 hours, P-value 0.75 at 12 hours and P-value 0.5 at 24 hours). Table 3 gives a summary of the significance tests for the difference in Sensor parameters assessed at the slit lamp, comparing each follow-up visit to the baseline visit at 5 minutes. Initially at baseline the quality of the Javal-keratometer mires reflected on the cornea, was sharp in 7 eyes (70%) and distorted in 3 eyes (30%). The lubrication status of the Sensor surface on slit lamp examination at baseline visit was good in 9 eyes (90%) and in one eye (10%) there were some hydrophobic spots seen. Conjunctival injection was absent in all but one study eye at baseline visit. The vertical centering of the Sensor at baseline visit was good in 3 eyes (30%) and in superior and inferior position in respectively 1 eye (10%) and 6 eyes (60%). The horizontal centering at baseline was good in 7 eyes (70%) while nasally and temporally displaced in respectively 1 (10%) and 2 (20%) eyes. In 3 subjects (30%) a lifted edge was observed at the Sensor margin that disappeared over time. Spontaneous mobility of the Sensor at baseline visit was fluid in 6 eyes (60%), difficult in 2 eyes (20%) and no movement was seen on slit lamp examination in another 2 eyes (20%). The push up test at baseline visit was fluid in 7 eyes (70%), but difficult in 3 (30%). For all these slit lamp parameters there were no significant changes over time except for mobility, both spontaneous and during push up test

(table 3). Mobility reduced rapidly over the follow-up visits and at the last visit no spontaneous mobility was present in 9 eyes (90%) and in one eye (10%) it was difficult, while the push up test was difficult for all eyes. Similar results were found for the subgroup of the 3 contact lens wearers (table 3). The Sensor was removed using gloves in 7 cases (70%), a glass rod in 2 (20%) and tweezers in 1 subject (10%). After removal of the Sensor 9 study subjects (90%) had limited localized fluorescein-positive corneal staining and 1 had generalized staining (10%). This was in the area of the telemetric microprocessor in 2 subjects (20%). As a measure of precaution ofloxacin antibiotics (Floxal ®) were prescribed in 3 cases (30%) for a corneal epithelial micro-defect, that resolved quickly. The border of the Sensor produced a fluorescein-positive impression on the limbal conjunctiva in 8 subjects (80%), covering more than 180 degrees in 5 subjects (50%). There was no change in the aspect of the upper tarsal conjunctiva, in comparison with the status before the Sensor wear. In 2 subjects (20%) a disconnection of the cable between the antenna and the recorder occurred during day time, resulting in no recording for one subject. In the other subject the disconnection could be solved, leading to a gap in the recording for only 2 hours. Figure 4 represents the signal of the Sensor recorded over 24 hours, expressed in arbitrary units (a.u.), with a close-up zoom during the day (zoom A) and night (zoom B). In all recordings the highest values were reached at night time when the participants were sleeping at home. A higher signal during both the middle of the night and early morning (12pm-6am) was registered in 75% of curves, including the contact lens wearers. A characteristic short-term signal drop was occasionally noticed and according to the subjects' log books this correlated well with exposure to sunlight during outdoor activities. The effect of blinking is visible in the detailed profile as a fraction-of-a-second peak (Zoom A). The absence of such

peaks over night is an indicator that they are blinking-related. Ocular pulsation could be seen in all curves. In Zoom B, showing the registration signal during 60 seconds at night, it can be seen that the ocular pulsation frequency is in line with that of cardiac activity. Only in one patient there were 4 episodes lasting 10 minutes each, without ocular pulsations visible. SENSIMED Triggerfish® was worn on average during 23.23 hours (SD 0.44, range 22.90-24.08). Repeating the analysis for the subgroup of 8 eyes that wore the Sensor for 24h +/- 1 hour showed the same probability results as for the whole group.

Discussion

Large IOP variations are an important risk factor that cannot be satisfactorily documented with the current available tonometers, especially when IOP peaks occur during the out-of-office hours [6, 8, 9]. These methods are prone to numerous potential sources of measurement error including eyelid closure, small precorneal tear film in dry eyes, accommodation, Valsalva maneuver, eye position, and body posture. Developing a device overcoming these drawbacks would be an important step forward in glaucoma management, by allowing assessment of therapy efficiency over a 24-hour period [9]. Our study evaluated the comfort and precision of the signal transmission during extended 24-hour Sensor wear in daily life on 10 healthy volunteers. In the vast majority of subjects a continuous transmission signal was recorded, indicating a good wireless power and data transfer by the telemetric chip and the antenna embedded in the Sensor during the 24-hour wear in humans. The technical shortcoming causing a disconnection of the cable between the antenna and the recorder was corrected after the study to avoid repetition in future. The

continuous presence of ocular pulsation on the recorded signal indicated a good monitoring quality. The episodes without ocular pulsations in one patient could be due to a failure in transmission of data from the Sensor through the wireless connection that may happen if the patient touches the orbital bandage with e.g. the hands. The highest signal values reached over night are in line with the reports of Liu et al on 24h IOP-recordings in healthy subjects[19] [10, 20-23]. However, these findings and the effect of sunlight exposure on the signal need to be confirmed by a larger series of 24-hour recordings. The Sensor was well tolerated over a 24-hour period, based on the comfort score, which remained high. There was no difference in score whether participants were regular contact lens wearers, co-workers or not. Furthermore, the fact that the corneal thickness did not vary significantly before and after device application indicated that no major corneal oedema or metabolic suffering occurred over the 24-hour wear. The observed temporary shift towards myopia can be partly explained by the corneal astigmatism induced by the Sensor impression at the corneo-scleral junction. Furthermore, there was a reduction in the vertical corneal radius seen after 24 hours. Nevertheless the change in cylindrical correction used during subjective refraction before and after Sensor-wear was not statistically significant, suggesting that other factors like visco-elasticity and biomechanics of the cornea, may contribute too. The MDD for the various parameters allowed to detect clinically important differences for most parameters, except for GAT where the study could only detect as significant a 2.58 mmHg change from baseline. Changes in comfort score of 2 grades was considered as clinically significant. The anterior surface wetting ability did not change significantly over 24 hours based on the quality of the Javal-keratometer mires image reflected on the cornea, but this needs to be confirmed by future studies using a tearscope. Best corrected visual

acuity was reduced during Sensor wear and this reduction remained statistically significant immediately after removal of the Sensor. This can be explained by the Sensor inducing some temporary corneal surface irregularities. The decentration of the Sensor in the vertical axis in 7 out of 10 subjects suggested a too tight fit, which could explain the reduction in the vertical corneal radius and be responsible for the corneal surface irregularities seen after 24-hour wear. The Sensor didn't move much, as based on the observed position of the telemetric microprocessor, the spontaneous mobility on blinking and the results of the push up test of the Sensor during the follow-up visits. Offering Sensors with different radii would definitely improve the fitting in the future, avoiding induction of significant corneal radius changes and therefore enhancing comfort and measurement precision.

Further trials remain to be done to discern the effect of true IOP changes from that of other variations on corneal radius of curvature as well as further detailed analysis of the recorded profile with respect to the influence of light exposure, Sensor fit and surface temperature.

In conclusion, this 24-hour, uncontrolled, open trial has encouraging results on the tolerability and functionality of the Sensor in human volunteers, but further controlled studies with different Sensor radii conducted on a larger study population are needed to improve comfort and precision. Trials to improve the interpretation of the telemetric signal are planned.

Acknowledgements

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Figures

Figure 1:

Ocular telemetric Sensor on the eye with the different parts indicated.

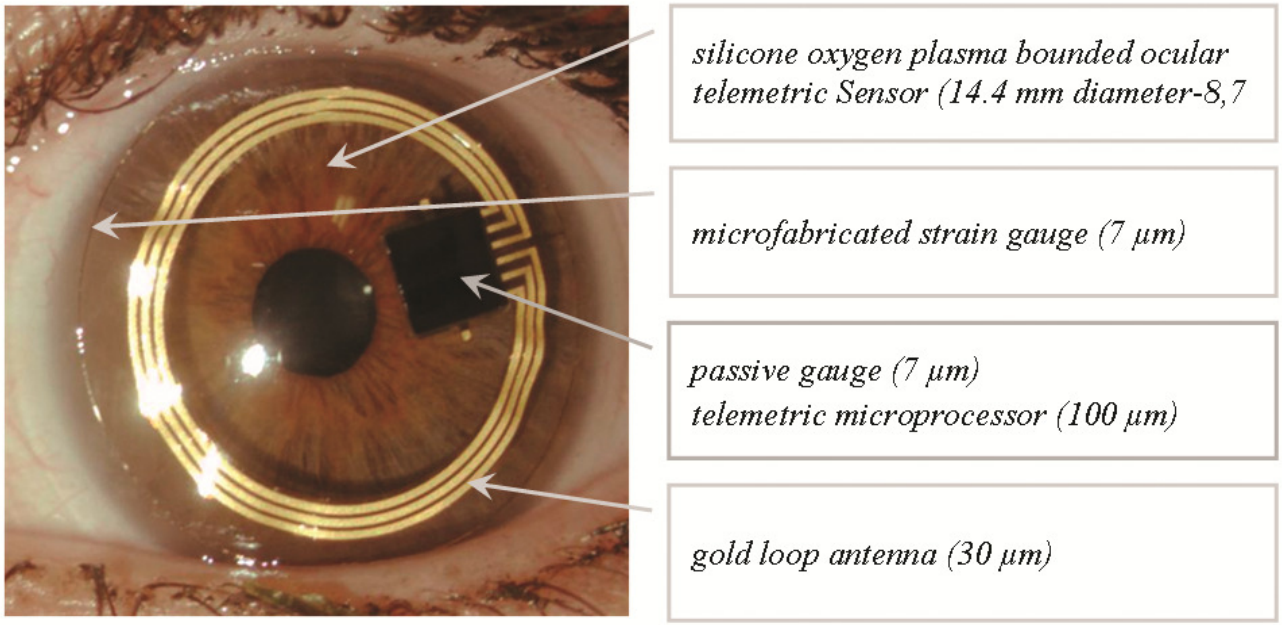

Figure 2:

The ocular telemetric Sensor transmits the information to a bandage-fixed periorbital loop antenna which is connected to a portable recorder worn around the volunteer's waist.

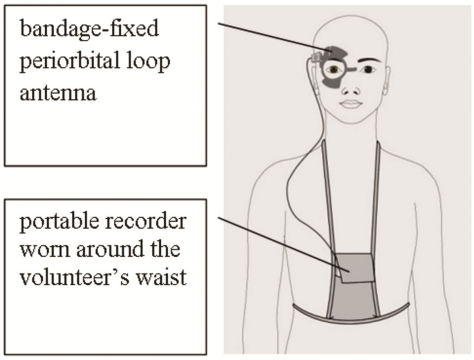

Figure 3:

Curve of the comfort score of the ocular telemetric sensor -wear over 24 hours with 95% confidence interval.

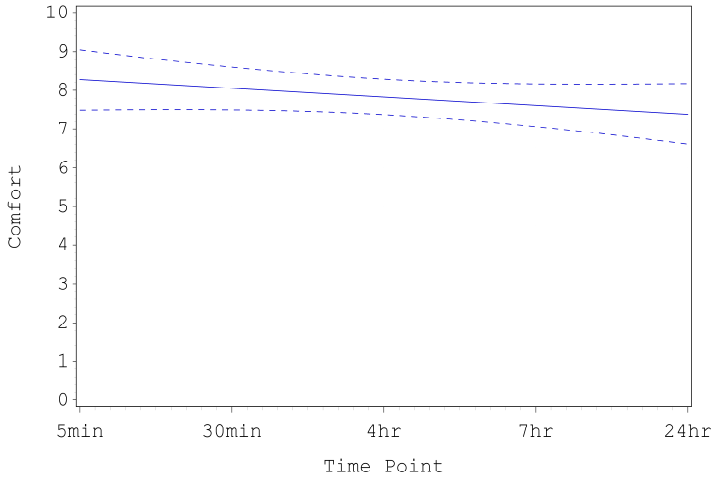

Figure 4:

Registration signal over 24 hours (expressed in arbitrary units [a.u.] output of the ocular telemetric sensor), with a close-up during the day (zoom A) and night (zoom B). Close-ups show output registration signal during 60 seconds.

Tables

Table 1: Baseline characteristics of 10 healthy volonteers, expressed in mean, standard deviation (SD), minimum (MIN) and maximum (MAX).

	MEAN	SD	MIN	MAX
age (years)	46,3	16,9	24	71
horizontal corneal diameter (mm)	11,7	0,3	11	12
palpebral aperture (mm)	10,8	1,3	8	12
pupillary diameter (mm)	5,5	1,1	3,5	7
cup/disc ratio	0,25	0,13	0,1	0,5
Goldmann intraocular pressure (mmHg)	14,7	3,3	10	20

Table 2: Evolution across the follow-up visits of the spherical and cylindrical correction and best corrected visual acuity in 10 volonteers, expressed in mean, standard deviation (SD), minimum (MIN), maximum (MAX) and P-value for the difference to the first visit.

	MEAN	SD	MIN	MAX	P-value
subjective spherical correction (Diopters)					
before Sensor wear	-0,88	1,93	-4,75	1,75	-
5 min	-0,18	1,56	-3,00	1,75	0,154
4 hours	0,13	1,94	-2,25	4,75	0,059
12 hours	0,10	2,18	-2,50	4,75	0,064
24 hours	0,10	2,26	-4,25	4,25	0,039
after Sensor removal	-1,90	1,88	-6,75	0,25	0,018
subjective cylindrical correction (Diopters)					
before Sensor wear	-0,55	0,50	-1,50	0,00	-
5 min	-1,08	0,58	-1,75	-0,25	0,074
4 hours	-1,00	0,49	-1,75	-0,50	0,047
12 hours	-1,00	0,62	-1,75	0,00	0,078
24 hours	-1,00	0,57	-1,75	0,00	0,063
after Sensor removal	-0,83	0,49	-1,50	-0,25	0,188
best corrected visual acuity (decimal fraction)					
before Sensor wear	1,07	0,18	0,65	1,20	-
5 min	0,56	0,21	0,15	0,85	0,002
4 hours	0,64	0,22	0,40	1,00	0,002
12 hours	0,61	0,26	0,25	1,00	0,002
24 hours	0,70	0,22	0,30	1,00	0,004
after Sensor removal	0,85	0,26	0,30	1,20	0,008

Table 3: Summary of the significance tests for difference in quality of the Javal-keratometry mires, wetability, conjunctival injection,ocular telemetric Sensor-centering and mobility spontaneously as well as on push-up test, compared to baseline visit (5 minutes after lens instillation), both in general and for optical contact lens wearers.

	P-values for change during the follow-up visits among all participants				P-values for change during the follow-up visits among contact lens wearers			
parameters	**after 30 minutes**	**after 4 hours**	**after 12 hours**	**after 24 hours**	**after 30 minutes**	**after 4 hours**	**after 12 hours**	**after 24 hours**
quality of Javal-keratometer mires	1,000	0,250	0,625	1,000	0,250	0,625	1,000	1,000
wetability	no change	1,000	0,500	1,000	no change	1,000	0,500	1,000
conjunctival injection	no change	0,500	0,250	0,063	no change	0,500	0,250	0,063
centering vertically	no change	1,000	0,500	0,250	no change	1,000	0,500	0,250
centering horizontally	no change	0,250	0,250	0,500	no change	0,250	0,250	0,500
spontaneous mobility	1,000	0,031	0,031	0,008	1,000	0,031	0,031	0,080
mobility at push-up	1,000	0,031	0,031	0,016	1,000	0,031	0,031	0,016

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