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Clinical comparison between a newly developed prototype method for measuring corneal sensitivity and the current gold standard

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Abstract

Purpose. The aim of the study was to test a newly developed prototype for corneal sensitivity measurement (liquid jet (LJ) with saline as stimulus) for repeatability and correlation with the Cochet-Bonnet esthesiometer (CB). This is an excerpt of a master thesis, which was part of a larger study.

Material and Methods. Corneal sensitivity thresholds (CST) were determined for 30 subjects, in a clinical trial with 30 subjects, with each device on two separate dates (with intervals of at least one day and a maximum of fourteen days). In addition, the pain sensitivity questionnaire (PSQ) was applied to determine any possible correlation with corneal sensitivity.

Results. Similar standard deviations of the CSTs for LJ and CB were obtained (LJ (M ± SD): 24.3 ± 2.0 dB; CB (M ± SD): 20.0 ± 2.0 dB). No statistically significant difference in CST was found between the two visits for LJ (mean difference: -0.063 dB, $p = 0.78$), however there was a statistically significant difference for CB (mean difference: -0.641 dB, $p = 0.003$). LJ CSTs correlated moderately positively with CB CSTs and PSQ (LJ-CB: $r = 0.476$, $p < 0.001$; LJ-PSQ: $r = 0.437$, $p < 0.001$).

Conclusion. LJ offers a significantly larger stimulus bandwidth than CB. Better reproducibility was observed for LJ, while correlation between the results for the two instruments was good. Significant moderate positive correlation was found between LJ CSTs and general pain sensitivity.

Keywords
esthesiometry, Cochet-Bonnet, Liquid Jet, prototype, PSQ

Introduction

The cornea has the highest nerve density in the body.[1-4] Based on animal models, it is estimated that the cornea is 300 to 600 times more densly innervated than the skin.[5] The nerves respond to mechanical, electrical, chemical and thermal stimuli to protect the functionality of the cornea.[1,4] However, if pain is not triggered due to a defect in the nociceptive system or the threshold value for triggering a reflex is too high, there is a risk of unnoticed injuries to the cornea and the associated possible loss of vision. An intact nerve supply is required to regenerate the cornea after injury and to maintain its integrity. Epithelial defects, ulcerations or even perforations of the cornea can occur if the response of the nervous system is interrupted for a long period of time.[6] Modern imaging methods have shown that structural anomalies occur with certain pathological defects and vice versa.[2,7] However, the structure and function of the nerves do not always match. Symptoms can be present without any visible pathology and a visible pathology can arise without presenting symptoms.[2,7] More precise measurements of corneal sensitivity could therefore provide additional information about the cause and effect of pathological defects on the corneal nerves.

Stimulus perception arises on the corneal surface, where it is passed on by the nerves to the truncus cerebri, interpreted by the limbic system and transmitted to the cerebrum. At each of these stages, the signal is either amplified or weakened by nociceptive processing. How unpleasant stimuli are perceived varies from person to person.[8] The Pain Sensitivity Questionnaire (PSQ) by Ruscheweyh et al.[9] is a validated process to auto-evaluate the individual perception of pain. This survey has already been used for eye examinations and has shown a connection between general pain perception and eye discomfort.[8,10,11] The PSQ was also proposed as an aid for the selection of suitable candidates for rigid contact lenses.[12]

Another function of superficial nerve endings is to detect cooling resulting from a thinned tear film and trigger the secretion of new tears and blinking, which distributes the tear film evenly again.[1,13] Thus, superficial, pain-sensitive nerves are jointly responsible for the basic secretion of tears and play an important role in the pathogenesis of dry eyes.[13]

Studies have shown that corneal sensitivity is not constant and can change as a result of systemic diseases such as diabetes,[14–16] surgical interventions on the eye[2,4] or aging processes.[17,18] Wearing contact lenses[19,20] and degenerative defects such as keratoconus also have a negative impact on the corneal sensation.[4,21,22] A change in sensitivity can explain the increased or absent symptoms in dry eyes, which means that symptoms may appear without any apparent reason and signs of dryness may be present without any symptoms.[1,13,23] The measurement of corneal sensitivity is therefore of great importance in ophthalmology. This measurement is carried out using aesthesiometry. Von Frey described aesthesiometry for the first time in 1894.[21] Back then, horse tail hairs of different lengths were used to test the sensitivity of the cornea. This method was optimised by Francheschetti in 1932 and then by Boberg-Ans by substituting the horse hairs with a nylon thread of constant diameter and variable length.[24] The length of the nylon thread is constrained to eleven values (from 0.5 cm to 6 cm, in steps of 0.5 cm); a very limited range with increasingly larger gaps in the measuring range as the thread length decreases. Furthermore, the nylon thread is susceptible to fluctuations in humidity.[25] Since the stimulus is visible, the patient's nervous state during the examination may also influence the threshold value. The pressure values for longer thread lengths are relatively close to one another and increase exponentially with decreasing thread length. When using a thread with a diameter of 0.12 mm, there is a risk of overlooking very high sensitivities, as the lowest threshold value for this diameter already corresponds to the average value of the thread with 0.08 mm in diameter. Furthermore, in the case of larger thread diameters, the high forces and the edges of the thread can lead to lesions on the corneal epithelium. For these reasons, the aesthesiometer with a thread diameter of 0.08 mm (Luneau Ophtalmologie, Chartres, France) was used in this study. It is worth noting that the Cochet-Bonnet aesthesiometer, with a nylon thread as a tactile stimulus, is the only commercially available device to measure corneal sensitivity. Due to the disadvantages of the traditional method mentioned above, a prototype (Liquid Jet aesthesiometer) was developed at the University of Applied Sciences of Northwestern Switzerland (FHNW), which uses a liquid stimulus consisting of saline solution.

The aim of this study was to compare the threshold value measurements of the corneal sensitivity obtained using the Liquid Jet aesthesiometer with those of the Cochet-Bonnet aesthesiometer and to test their repeatability. Additionally, the threshold values for corneal sensitivity were tested for correlation with the results from the Pain Sensitivity Questionnaire (PSQ). This article is a subanalysis of a larger study at the Institute for Optometry of the FHNW.

Material and Methods

Test subjects

The participating test subjects were recruited from the patient pool of the Institute of Optometry of the FHNW and by advertisement. Subjects aged between 18 and 30 years (Group A) or 50 and 70 years (Group B) were admitted to the study (**Table 1**). The division into two age groups was based on the decreasing density of nerve cells and the associated reduction in the sensitivity of the cornea with age.[17,18] According to Acosta et al., gender has no significant influence corneal sensitivity.[18] However, wearing rigid contact lenses was an exclusion criterion from the study due to their lasting influence on corneal sensitivity, whereas soft contact lenses were allowed to be worn but had to be removed at least 48 hours before the examination.[19,20] Subjects could not present any systemic diseases that may have an impact on eye health, such as diabetes. Subjects, who have experienced trauma or operations, as well as acute inflammatory processes affecting the anterior eye segment and with symptoms of dry eye (OSDI

Table 1: Age distribution of the study participants

		General		Age group A		Age group B	
		Men	Women	Men	Women	Men	Women
Number		18	12	9	9	9	3
Age [years]	Mean	42.2	31.3	24.2	22.6	60.2	57.3
	Standard deviation	± 18.9	± 16.2	± 2.8	± 3.0	± 6.5	± 9.0

score > 13) were also excluded. Furthermore, and especially on the day of the examination, no systemic drugs or eye drops which could influence the tear film, were allowed to be used.

This study is a subanalysis of a larger study, which was carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Northwestern and Central Switzerland (project ID 2019-012).[26]

Devices for measuring corneal sensitivity

Cochet-Bonnet aesthesiometer

In the 1960s, Cochet and Bonnet improved the existing aesthesiometer by developing two models with different thread diameters (0.12 and 0.08 mm). The length of the nylon thread is variable and adjustable in 0.5 cm increments. The procedure foresees the application of the thread perpendicular to the central cornea until it bends five degrees. For the measurement, the test subject concentrates on a distant fixation target and states whether the stimulus caused by the thread was felt. The length of the thread that caused the last stimulus felt by the test subject is noted in centimetres (cm).[24] The aesthesiometer used in this study had a thread diameter of 0.08 mm (Luneau Ophtalmologie, Chartres, France).

Liquid Jet aesthesiometer prototype

The newly developed Liquid Jet aesthesiometer prototype (LJ) (self-made by FHNW, updated version as of September 2019) consists of a camera-centring device, a peristaltic pressure pump, a pressure transmitter, a valve (with a diameter of 0.1 mm) with a connected heating foil and two release buttons. In this case, the stimulus consists of an isotonic saline solution released during a valve-opening period of 40 ms. The isotonic saline solution reaches the valve in a sterile manner through an infusion kit and from there is projected onto the cornea with a predefined intensity and temperature. The volume of the saline solution is so small, that it is absorbed by the tear film immediately after hitting the front surface of the eye and does not overflow beyond the eyelid margin (0.61 ml for 150 mbar to 3.45 ml for 1500 mbar). Measurements conducted by Bistoletti and Mauchle within the scope of a Bachelor thesis at the Institute of Optometry of the FHNW showed that a maximum cooling of the surface of the cornea of 1.63 °C can be assumed.[27] Thus, for this study, stimulus temperature was set at 2.2 °C warmer than ocular surface temperature of the cornea to ensure that any cooling occurred below the tolerance level. A cooling of as little as 0.1 °C may trigger excitation of the cold-sensitive receptors, whereas the sensitivity to an increase in ocular surface temperature is much lower.[1,28,29] The mean stimulus temperature was 36.7 ± 0.6 °C. By controlling the temperature of the stimulus to attain a similar temperature to that of the surface of the cornea, it was aimed to present a pure tactile stimulus.

The measurement procedure took place as follows. The test subject fixates a point light source while the opposite eye is occluded. Two laterally offset cameras enable the correct centring of the device and its required distancing of 15 mm from the eye. The measurement is carried out in a darkened room so that the test subject cannot visually perceive the stimulus, as this may influence the response (felt/not felt).

The required settings are configured using a laptop connected to the aesthesiometer. The pre-programmed algorithm searches for the corneal sensitivity threshold in a step-by-step process. This is achieved by alternating between continuously reducing clearly perceptible stimuli and continuously increasing stimuli that are not perceptible. This prevents any possible bias of the examiner. After the stimulus was released, the test subject indicates by pushing a button whether he or she felt the stimulus on the eye. The device is cleaned after each test subject using a rinsing process and ultrasonic cleaning of the valve.

OSDI

The Ocular Surface Disease Index (OSDI) is determined with the help of the Allergan questionnaire, specially developed and validated for this purpose.[30] The test subject fills in the survey and the answers are used to assess whether a person has subjectively dry eyes or not. The questionnaire consists of twelve questions related to the everyday routine of the last week and covers the most common activities that typically involve dry eye symptoms. The OSDI score is calculated on the basis of the sum of the values of all answered questions. An OSDI score of 13 represents the lower limit for dry eyes.

Pain Sensitivity Questionnaire (PSQ)

The questionnaire consists of 17 questions about everyday situations, which are to be rated on a scale from zero (not painful at all), one (barely perceptible) to ten (the strongest imaginable pain). This results in a Painscore ranging from zero to ten.[9]

Study design and examinations

The present study is designed as a prospective clinical trial with repeated measurements. Two threshold values were measured with the LJ and CB techniques respectively during both subject visits. All measurements were performed exclusively on the right eye, with the last measurement of each appointment being the one with the Cochet-Bonnet aesthesiometer, since this procedure may cause superficial epithelial corneal defects and, thus, falsify any following measurements.

Each test subject attended for two visits of approximately 60 minutes. During the first visit, the test subjects were informed in detail about the procedure. After signing a declaration of consent, the test subjects completed the OSDI questionnaire and the Pain Sensitivity Questionnaire (PSQ). Both eyes were checked for acute inflammation or previous trauma/operations by checking the medical history of the patient and via a slit lamp examination of the anterior eye segment.

A subliminal and a clearly noticeable stimulus were demonstrated in the left eye using both measuring devices so that the test subjects knew what to expect. This was followed by the two determinations of the corneal sensitivity threshold value. At the end of the measurements, the anterior eye segment was examined again with the slit lamp, now with the additional use of fluorescein. The threshold value determinations and the completion of the questionnaire were repeated at intervals of at least 24 hours and a maximum of 14 days.

Statistical analysis

The data were processed with Microsoft Excel 2019, converted, and then evaluated with IBM SPSS 25.0. The data were then checked for normal distribution with the Shapiro-Wilk test. The mean values for normally distributed data were compared using either the t-test for paired samples or the t-test for independent samples. The non-normally distributed data were tested with a non-parametric test for dependent samples (Wilcoxon test) or a non-parametric test for independent samples (Mann-Whitney U test). The linear regressions were calculated using the Pearson correlation.

Method repeatability was assessed with use of Bland-Altman plots (**Figure 4** and **Figure 5**).[31] First, the difference between the threshold values from the first and the second visit was calculated. The mean values, the standard deviations and the 95 % confidence intervals were also determined. The confidence interval is calculated by multiplying the standard deviation by ± 1.96 and adding it to the mean. The x-axes of the plots correspond to the mean and the y-axes to the differences. The red line represents the mean, and the green lines reflect the upper and lower ends of the 95 % confidence interval. The width of the confidence intervals shows the reproducibility of the respective procedures. The closer the confidence intervals are to one another and the less the mean deviates from zero, the better the reproducibility of the respective method.

In natural sciences, the signal-to-noise ratio is used to assess the quality of a measured variable. The mean of the threshold values of the first and second visit was taken as the signal and the standard deviation was calculated. The noise was calculated from the standard deviation of the difference between the threshold values of the first and second visit. The signal-to-noise ratio is a measure of the usability of the method.

The calculations presented here are general, i.e., the data was not subdivided according to age. Furthermore, we used a significance level of $\alpha = 0.05$. Values of $0.05 < p < 0.2$ were taken as presenting a strong or a less strong trend respectively. The correlation coefficients were interpreted according to Cohen, where $r = 0.1$ corresponds to a weak, $r = 0.3$ to a moderate and $r = 0.5$ to a strong correlation.[32]

Data transformation

Data with different units of measurement cannot be directly compared without undergoing a prior transformation. Therefore, the threshold values were transformed into a logarithmic scale. Decibel (dB) is a ratio of two numbers based on a logarithmic scale. This unit of measurement allows very large or very small values to be displayed and processed more easily. In order to avoid negative values, 1 mbar or 1 µN respectively were selected as zero values of the dB scale.

Results

Testing for normal distribution

Differences between the measured values from the first and second appointments were tested for normality, using the Shapiro-Wilk test. After transforming the threshold values into decibels, the null hypothesis of normal distribution for LJ could be accepted ($p = 0.828$). However, the null hypothesis of normal distribution was rejected for the CB thresholds ($p = 0.001$). The null hypothesis of normal distribution was also rejected for OSDI and Painscore (OSDI: $p < 0.001$; Painscore: $p = 0.006$).

Overview of the threshold values

The means (M) of the threshold values and their standard deviation (SD), as well as the median (MD) over all test subjects, are summarised in **Table 2**. The threshold values are listed in mbar or µN, and dB. Additionally, **Table 2** also shows the first and third quartiles, which describe the magnitude of the interquartile range. LJ has higher mean values than CB, with the SD being very similar for both methods.

Comparison of visits

The threshold values of the first and second visits were analysed with the t-test for paired samples for the LJ method and with the non-parametric test for dependent samples (Wilcoxon test) for the CB method.

Table 2: Threshold values for the Liquid Jet and Cochet-Bonnet esthesiometers

	Liquid Jet		Cochet-Bonnet	
	dB	mbar	dB	µN
Median	24.2	264.1	19.3	85.7
Mean	24.3	302.5	20	114.2
Standard deviation	2	143.4	2	74.9
First quartile	23	198	18.4	69.8
Third quartile	26	402.5	21.3	135.5

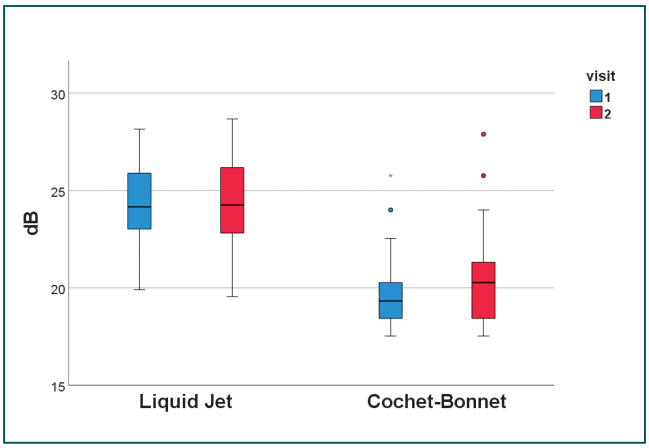

Figure 1: Box plots of the threshold values grouped by appointment

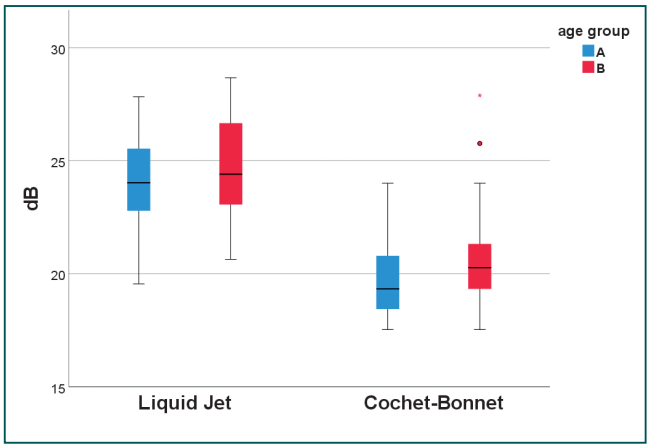

Figure 2: Box plots of the threshold values grouped by age group

For LJ, there was no significant difference between the visits for any of the age groups (LJ general: M difference = -0.063 dB, p = 0.779; group A: M difference = +0.112 dB, p = 0.704; group B: M difference = -0.325 dB, p = 0.359). In the case of CB, however, there was a significant difference between the threshold values of the two visits when considering all test subjects and when only considering age group A (CB general: M difference = -0.641 dB, p = 0.003; group A: M difference = -0.576 dB, p = 0.020). For age group B, there was a strong tendency towards different threshold values between the two visits (M difference = -0.739 dB, p = 0.072) (**Figure 1**).

Comparison of the age groups

The means of the threshold values were slightly higher in age group B than in age group A. In the case of LJ, this difference between the two age groups was not significant (p = 0.324). For CB, the difference between the two groups showed a slight trend towards higher measured values in the older group (p = 0.151) (**Figure 2**).

Correlations

The correlations were calculated using the Pearson product-moment correlation coefficient and checked for significance. The LJ measurements correlate moderately positively with the CB and Painscore measurements (**Figure 3**).

Repeatability

Both LJ and CB showed slight fluctuations in their signal quality and a slightly weaker noise for CB. This leads to a low signal-to-noise ratio, both with and without subdivision into age groups (see **Table 3**). The differences between the two visits were not significantly different for LJ, whereas there was a significant difference for CB (LJ general: p = 0.779; CB general: p = 0.003). The difference between the two measurements averaged to -0.063 ± 3.396 dB for LJ and -0.641 ± 3.091 dB for CB (**Figure 4** and **Figure 5**).

Table 3: Signal and noise of the two measurement methods

		General		Group A		Group B	
		Standard deviation [dB]	Ratio	Standard deviation [dB]	Ratio	Standard deviation [dB]	Ratio
Liquid Jet	Signal	1,87	1,08	1,75	1	2,03	1,2
	Noise	1,73		1,75		1,7	
Cochet-Bonnet	Signal	1,85	1,17	1,67	1,1	2,03	1,21
	Noise	1,58		1,52		1,69	

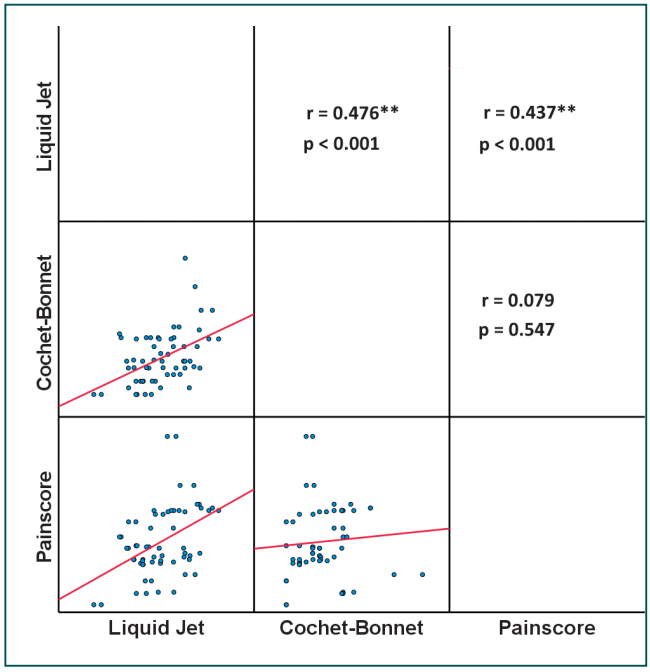

Figure 3: Scatter plots of the measured parameters

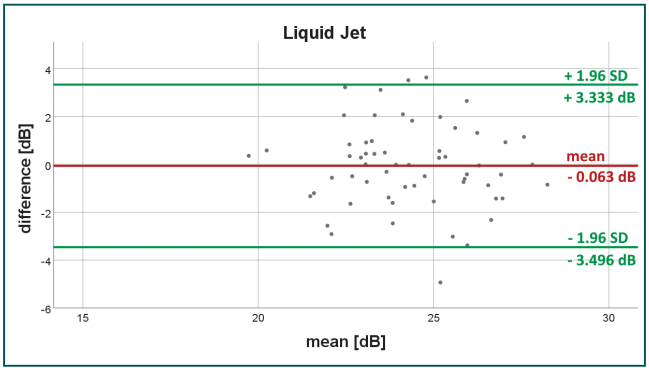

Figure 4: Bland-Altman plot for the Liquid Jet esthesiometer

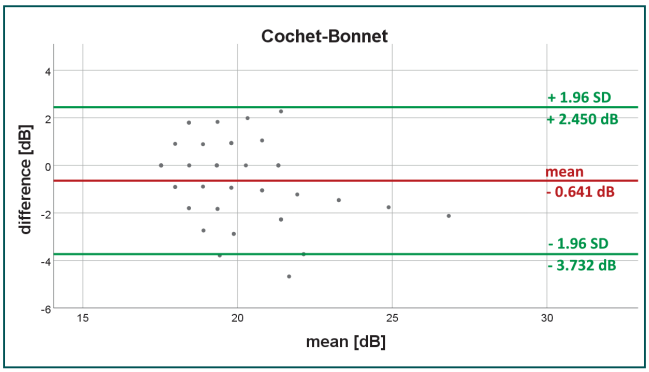

Figure 5: Bland-Altman plot for the Cochet-Bonnet esthesiometer

Discussion

The aim of this work was to find out whether the Liquid Jet aesthesiometer prototype delivers repeatable values and correlates with the values of the Cochet-Bonnet aesthesiometer. In addition, we also tested a clinical application of the prototype.

General comparison

The fluctuations in the measurements with the Liquid Jet and the Cochet-Bonnet aesthesiometer turned out to be similar when considering the overall subject group and when considering the two age groups.

Comparing the two age groups, a tendency towards a higher threshold value in the older group was observed, which however, was not statistically significant. This trend was only statistically significant in the measurements obtained with the Cochet-Bonnet aesthesiometer. Roszkowska, et al. also found significant differences between the age groups in their analysis with the Cochet-Bonnet aesthesiometer.[33] However, this difference was not significant for the Liquid Jet aesthesiometer, probably due to the large difference in sample size (Roszkowska et al. 500 eyes versus 30 eyes). The age groups in this subanalysis are not homogeneous, which makes a comparison difficult. However, due to changes in corneal sensitivity with age, it was considered important to maintain

this division. In the larger study with sample size determination, which has not yet been published, this difference was also significant for LJ.

With the Liquid Jet aesthesiometer, the pressure between the stimuli is regulated by a peristaltic pump, a process which takes a relatively long time. Even if a successful measurement can be carried out within three to five minutes with appropriate compliance of the test subjects, this time interval is much longer than the one required with the Cochet-Bonnet aesthesiometer. The installation of an irrigation pump would be a possible optimisation to accelerate the build-up of the required pressure.

Correlations

The threshold values of the Liquid Jet aesthesiometer have a moderately significant positive correlation with those of the Cochet-Bonnet aesthesiometer ($r = 0.476$, $p < 0.001$). This suggests that these two methods can measure similar values.

On the other hand, OSDI and Painscore hardly correlate with the other variables. This is possibly due to the fact that only subjects with a low OSDI, i.e., with no dry-eye symptoms and healthy eyes, were admitted to the study. Only the Liquid Jet had a moderately significant positive correlation with the general pain sensitivity from the PSQ ($r = 0.437$, $p < 0.001$). Since the Cochet-Bonnet aesthesiometer correlates with Liquid Jet, but not with Painscore, these correlations would have to be examined more closely with a larger sample. According to Ruscheweyh et al., PSQ scores significantly correlated with the assessment of perceived pain, but not with the individual threshold values. They found no significant differences in gender or age in their validation of the PSQ.[9]

Repeatability

When comparing sensivitiy thresholds from the first and second visit, significant differences were observed with the Cochet-Bonnet aesthesiometer ($p = 0.003$). This was not the case with the measurements performed with the Liquid Jet prototype ($p = 0.779$). These observations apply both with and without a subdivision into the two age groups. The reasons for the differences between the two visits may, on the one hand, be due to the fact that these are psychophysical measurements at the limit of perception, which generates variability, and, on the other hand, to the fact that physiological daily differences are, indeed, possible. There is significant noise in the measurements obtained using both devices. This high level of noise leads to a very low signal-to-noise ratio for both measurement methods. However, it cannot be conclusively stated whether the noise has a physiological source stemming from the fact that all test subjects had healthy eyes, or it is due to the measurement inaccuracy of the devices.

The authors of this study believe that the repeatability of measurements obtained using the Cochet-Bonnet aesthesiometer is very likely overestimated. Due to the limited stimulus range and the uneven intensity distribution of the stimuli, this measurement method is a lot more tolerant to fluctuations than the infinite number of intensity levels of the prototype.

Conclusion

By controlling the temperature of the stimulus to attain a similar temperature to that of the surface of the cornea, the Liquid Jet aesthesiometer aims to deliver a true tactile stimulus. The measurements were found to be repeatable and correlated with the Cochet-Bonnet aesthesiometer, which is currently still used as the gold standard. The Liquid Jet aesthesiometer has a significantly larger stimulus rage, making it possible to recognise smaller sensitivity fluctuations and to determine the corneal sensitivity in a more repeatable manner.

The Liquid Jet aesthesiometer has a moderately significant positive correlation with general pain perception ($r = 0.437$, $p < 0.001$). This potential connection would have to be examined more closely in the future with a larger sample.

Further studies with optimised prototypes and a larger test sample with balanced age groups and, if necessary, test subjects with dry-eye symptoms should be conducted in the future.

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