Feasibility and Safety of a Coaxial Dual-Wavelength Optical Coherence Tomography Apparatus

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Keywords

Dual-color imaging · Optical coherence tomography, spectral-domain · Retina

Abstract

Purpose: To evaluate the feasibility and safety of a coaxial dual-wavelength optical coherence tomography (OCT) device (marked as Hydra-OCT). **Methods:** Healthy participants without ocular pathology underwent retinal imaging using the Hydra-OCT allowing for simultaneous measurement of retinal scanning of 840 and 1,072 nm wavelength. Before and after measurement, best-corrected visual acuity and patients' comfort were assessed. Representative OCT images from both wavelengths were compared by 5 independent graders using a subjective grading scheme. **Results:** A total of 30 eyes of 30 participants (8 females and 22 males) with a mean age of 26.5 years (range from 19 to 55 years) were included. Dual-wavelength image acquisition was made pos-

sible in each subject. The participant's effort and comfort assessment using the Hydra-OCT imaging revealed an equivalent value as compared to the commercially available OCT machine. No adverse events were reported, and visual acuity was not altered by the Hydra-OCT. Imaging between the systems was comparable. **Conclusions:** This study provides evidence for the feasibility and safety of a coaxial dual-wavelength OCT imaging method under real-life conditions. The novel Hydra-OCT imaging device may offer additional insights into the pathology of retinal and choroidal diseases.

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Introduction

Optical coherence tomography (OCT) is a noninvasive in vivo imaging technique based on reflected light due to boundaries of different refractive index of the tissue to produce detailed cross-sectional and three-dimen-

sional images [1, 2]. Over the past decade, several innovations in the OCT techniques [3–5] have led to significant improvements in the assessment of ophthalmic patients especially for retinal diseases [6]. Thereby, OCT data have been established as an outcome measure for clinical trials as well as for the diagnosis and follow-up of ophthalmic patients [7].

Since 2012 most of the commercially available OCT devices have been line-camera-based spectral-domain OCT (SD-OCT) systems [8] operating with a wavelength of around 800 nm allowing for a tremendously higher sampling rate and improved signal-to-noise ratio compared to the previously used time domain OCT technique [9, 10]. To compensate for the lack of deep tissue penetration due to the short wavelength of SD-OCT, the technique of enhanced depth imaging [11, 12] utilizing the depth-dependent sensitivity of frequency domain OCT was introduced in order to visualize deeper structures. The wavelength scanning frequency domain technology, swept-source OCT [13] (SS-OCT), operates at a wavelength of 1,070 nm, which ameliorates the depth penetration of the tissue [14] and improves sampling speed for a more comprehensive visualization of the choroid [15, 16]. Longer wavelengths provide refined deeper tissue information [17]. In contrast shorter wavelengths produce higher contrast in superficial tissue.

As the retinal pigment epithelium, Bruch's membrane and the choroid represent a coadjutant functional complex [18], the combination of the advantages of both imaging techniques and respective wavelengths might be aimed for. Up to now, the investigation of ophthalmic patients with both imaging techniques could only be carried out by separate application of at least two OCT devices.

To overcome this drawback, an extended SD-OCT device (Hydra-OCT) was developed that incorporates two different but coaxially aligned wavelengths. We aimed to compare the Hydra-OCT imaging system to a commercially available SD-OCT device with regard to the feasibility, subject comfort and safety in order to allow for future application of the technique in experimental and clinical settings.

Methods

This study was designed as a prospective, open-label, nonrandomized investigation.

Intended Use

The overall objective of this study was to obtain and assess the feasibility, safety and patient comfort of Hydra-OCT compared to

the established SD-OCT. Specific aspects of the Hydra-OCT prototype, such as diagnostic performance and monitoring differences between the devices, were not assessed during this preliminary study.

Subjects

Healthy volunteers were prospectively recruited for this study and investigated at the Department of Ophthalmology at the University Hospital Basel, Basel, Switzerland. Inclusion criteria were compliant subjects with a minimum age of 18 years or older, German-speaking, clear optic media and without any ocular pathology that were evaluated during a slit lamp examination. Exclusion criteria were coexisting accompanying diseases such as epilepsy, dementia, Parkinson's disease, serious mental health illness, developmental disability or cognitive impairment, general disability that would preclude adequate comprehension for the informed consent, subjects who did not sign informed consent and subjects using electronic medical devices (e.g., hearing aid, cochlear implant, pacemaker, defibrillator).

Sample Size Calculation

The usability literature indicated that 30 eyes would be an appropriate number [19].

Data Quality Assurance

For each participant enrolled in the study, an anonymized case report form (CRF) was completed and signed by the primary investigator. Participant identities were coded using a participant identification number. Data analysis and outcome evaluation were performed with anonymized data, and no other blinding procedures were applied.

Conduct of the study was fully documented, and the study data were subsequently verified as required by ISO 14155 and local regulations. Any CRF entries and corrections were performed by the site's staff members and authorized by the primary investigator. The entries were therefore checked by a study nurse and any errors or inconsistencies could then be clarified. At the end of the study, the study nurse collected original, completed and signed CRFs, and their copies were stored on the study site.

Dual-Color Imaging

The Hydra-OCT (Fig. 1) is constituted of a dual-wavelength coaxial SD-OCT prototype and was developed at the Institute for Human Centered Engineering optoLab, University of Applied Sciences, Biel, Switzerland, as the commercial-grade successor of a device used in a different study in Hong Kong [20], in close collaboration with the Department of Ophthalmology, University Hospital Basel, Basel, Switzerland, and the Institute of Molecular and Clinical Ophthalmology Basel, Basel, Switzerland.

Two superluminescent diodes emitted concurrently, but independently of each other, laser light with a central wavelength of 840 (± 15) nm and 1,072 (± 20) nm, respectively. The bandwidth was 48 (± 12) and 103 (± 15) nm, respectively. The lasers were classified as group 1 device according to EN ISO 15004-2:2007 and class 1 laser according to IEC 60825-1. The Hydra-OCT fulfilled all terms and conditions of light hazard of EN ISO 15004-2:2007 according to group 1 and has been reviewed and cleared by independent investigations with regard to laser and electromagnetic safety.

The light beam of the 1,072-nm light source was coupled into the light path of the commercially available OCT device (Spectralis

Fig. 1. Representation of the Hydra-OCT with two laser sources enhancing a standard Heidelberg OCT scanner with a 1,072-nm module. **a** The standard scanner was extended optomechanically with a housing containing the coaxial laser unit. **b** Interior view of the additional laser unit with feeding light source. **c** Cross-section OCT of a healthy retina with the standard 840-nm scanner wavelength (Heidelberg Spectralis SD-OCT). **d** Co-spatiolocalized, additional image information gain by second spectral-domain laser scanning system using a 1,072-nm laser beam.

HRA + OCT, Heidelberg Engineering, Heidelberg, Germany). The two OCT beams utilized the same scan geometry with a well-specified retinal offset separation in scan direction of 60 μm for eye safety reasons. The backscattered light from the retina was directed to two different spectrometers dedicated to the corresponding wavelengths. The Hydra-OCT had a scan length of 5 mm and high sample resolution of 400 pixels with an A-scan rate of 15 kHz, and averaging of maximal 22 B scans was possible at this time. Spectralis OCT single-line acquisition had a resolution of 768 pixels, with automatic real-time tracking averaging of 25 B scans and excluding the technique of enhanced depth imaging (enhanced depth imaging off) which is a recent modification of the standard technique of image acquisition to better display the structural details of the choroid.

Clinical Investigation Safety End Point

To determine safety performance of the Hydra-OCT, any adverse events, serious adverse events and/or serious adverse device effects were to be collected, fully investigated and reported once they occurred in the course of the study. In addition, best-corrected visual acuity (VA) was measured before and after the Hydra-OCT imaging using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. In the case of a decrease in individual VA, an additional VA assessment was performed 10 min after the Hydra-OCT measurement in order to exclude simple blinding effects.

Concerning participants' comfort during the Hydra-OCT examination, a specified questionnaire was used giving values from 0 to 100 (with 0 being a very uncomfortable investigation and 100 being a very comfortable one, respectively); see online supplementary Table S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000508751) for the electronic CRF.

Theoretically, an OCT examination can temporarily reduce the VA due to examination side effects such as a laser impact or dry eyes when patients do not blink enough. The safety end point has been formulated as the change in letters logMAR (logarithmic minimum angle of resolution) measured using an ETDRS test chart. One letter on the chart is 0.02 logMAR units. The VA was measured before and after the examination with the Hydra-OCT. If the difference in the VA score decreased by more than 0.1 logMAR (change of more than 5 letters), as measured before and after the OCT imaging, a repeated measurement was taken 10 min later to exclude temporary side effects or simple dry eye problems. In cases where the remeasured VA difference was still greater than 0.1 logMAR, the primary investigator was to examine the eye for adverse events and take appropriate measures, if necessary.

Feasibility and Image Comparability

For the primary end point, a true/false criterion was explored with regard to the feasibility of the Hydra-OCT, on whether both wavelength scans could be recorded.

A commercially available SS-OCT device (DRI OCT-1 Atlantis, Topcon, Tokyo, Japan) was used to compare feasibility, subject's comfort and safety. The SS-OCT scan pattern was defined by the manufacturer's software using a single-line B scan of 6 mm length. There was no subsequent VA assessment after the SS-OCT measurement as the device had already been approved for clinical use and no such changes had been reported till the time of the measurements.

Statistical Analysis Methods

Frequencies and proportions related to successful measurements were computed, along with the mean value and standard deviation for the duration of the OCT examination performed by using the Hydra-OCT. Before and after each examination, a change in the VA score was calculated for each examined participant. The data were exported as indexed lists in the software package R [21]. Patient comfort during each OCT scanning was recorded and analyzed. Comparisons between pre- and post-VA are assessed using a Wilcoxon signed rank test. A p value <0.05 was considered as significant.

Image Comparability between 840- and 1,072-nm Imaging

After the Hydra-OCT measurement had been performed, the central foveal B-OCT scans were independently reviewed and compared to the standard SD-Spectralis B scan of the corresponding location by 5 blinded medical retina specialists (P.W.H., S.R., P.M., J.Z., C.E.). Since the study only dealt with the feasibility of the new device, a simplified grading was carried out [22]. The results were considered a "comparable" (marked as 1) if all the retinal layers and the choroid could be identified in both displayed images from the same eye. In cases when the layers could not be differentiated, the outcome was considered a "fail" (marked as 0). In addition, each image was rated with an individual score and then the total score was calculated for the image category.

A statistical analysis was performed to compare the quality of images acquired by the Hydra-OCT and Spectralis devices. First, the binary assessments of the 5 individual graders were combined into one consensus as follows: if a majority of the graders judged an image pair as "comparable," it was set to "comparable" in the consensus. Otherwise, it was set to "not comparable." The consensus consists of 28 "comparable" and 2 "not comparable" image pairs. Subsequently, we performed a one-sided Fisher's exact test for count data with the null hypothesis that all image pairs are comparable. Fisher's exact test for count data can be used to assess the association between two classifications. In our case, this is the observed classification in "comparable" (28) and "not comparable" (2) image pairs and the hypothesized classification in "comparable" (30) and "not comparable" (0) image pairs.

Results

Patient Demographics

A total of 30 eyes from 30 participants (27% females [$n = 8$] and 73% males [$n = 22$]) who met the inclusion criteria were recruited for OCT retinal examination by both the investigational Hydra-OCT and the reference spectral OCT device. The overall mean age was 26.5 years

Fig. 2. Box plot of the participant's rating of patient comfort. The rating was performed by assessing the comfort of the investigation on a scale of linear values from 0 to 100 with 0 being a very uncomfortable investigation and 100 being a very comfortable investigation, respectively. The median score was 70 and the interquartile range consisted of a score of 52.5 for the first quartile and 80 for the third quartile, respectively. The minimum score for patient comfort was 30, and the maximum was 95 out of 100. The results indicate a well-tolerated Hydra-OCT examination that is comparable to a commercially available OCT device.

(range from 19 to 55 years). The mean age of female patients was 28.5 years (range from 21 to 55 years) and of male patients 26.0 years (range from 19 to 55 years, respectively).

Secondary End Point

The patients' narrative feedback on their comfort during each OCT imaging procedure was documented and summarized in Figure 2. In total, comfort assessments from all 30 patients were obtained. The median and interquartile range of patient comfort was 70.0 (52.5–80.0).

Safety End Point

One patient showed a VA decline after Hydra-OCT device investigation of one ETDRS line. After 10 min the VA testing was repeated, and VA returned to normal. Neither safety concerns as defined by VA loss nor adverse effects, serious adverse effects or serious adverse device effects were observed. The descriptive statistics of the comparison of the pre- and postinvestigational VA is summarized in Figure 3.

Intercolor Image Comparability

The one-sided Fisher's exact test for count data revealed a p value of 0.2458. That is, our observed classification of "comparable" (28) and "not comparable" (2) image pairs is not significantly different from the hypothe-

Fig. 3. Box plot of visual acuity (VA) ETDRS score before (pre) and after (post) examination with Hydra-OCT. The assessment was performed using an ETDRS chart. The median score of the measurement of the VA before the examination was 58, and the interquartile range consisted of a score of 53.0 for the first quartile and 59.8 for the third quartile, respectively. The minimum score was 47, and the maximum was 65. After the examination, the median score of the measurement of the VA was 58, and the interquartile range consisted of a score of 54.2 for the first quartile and 60 for the third quartile, respectively. The minimum score was 49, and the maximum was 65. The exact Wilcoxon signed rank test showed no significant change of VA before compared to after the examination ($p = 0.005007$).

sized classification of “comparable” (30) and “not comparable” (0) image pairs. We found that Spectralis images did not get significantly better judgments than Hydra-OCT images.

Discussion

OCT has become one of the most important imaging methods for diagnosis and monitoring in a number of diseases such as age-related macular degeneration [11, 23], diabetic retinopathy [24, 25] and central serous retinopathy [26, 27], among others. Novel insights were mainly driven by technical enhancements such as enhanced depth imaging OCT [28, 29], swept-source OCT [30, 31] or optical coherence tomography angiography [32, 33]. Currently, most of these OCT devices are operating using a single wavelength.

The aim of this study was to assess patient comfort and image content equivalence of a recently developed OCT instrument compared to commercially available OCT technologies: The proposed OCT device is based on a commercial OCT device where a Heidelberg Engineering Spectralis (840 nm wavelength) has been extended to in-

sert a second coaxial beam path to introduce a second beam at 1,072 nm. No difference was seen with respect to VA. The subjects reported a comfort at least equivalent to that of a commercially available swept-source OCT device. One patient had transient vision decline of one ETDRS line after the Hydra-OCT measurement. VA returned to normal after 10 min. The patient reported a dry and slightly irritated eye after the measurement which was considered the reason for the vision decline. The performed safety tests did not indicate any patient risks.

In this context, this study demonstrated the successful integration of a novel scanning concept by combining two different wavelength ranges (centered at 840 and 1,072 nm, respectively) in a single OCT device.

The evaluation of the obtained cross-sectional retina images showed a high agreement between the graders who reported that the provided scans were at least similar between the wavelengths. It was interesting to note that the SD-OCT images showed some degree of a blurred image probably due to the averaging of multiple B scans (Fig. 1). Hydra-OCT images, on the other hand, showed a delicate appearance even in the superficial structures such as the optic disk vessels. The quality of deeper areas like choroidal structures were comparable between the two wavelengths.

The ability of light to penetrate scattering tissue is especially depending on the wavelength [34]. Longer wavelengths are able to penetrate more deeply compared to shorter ones [35, 36]. This allows a more profound investigation of the choroid and even the sclera [37, 38].

Furthermore, an examination bringing the advantage of two simultaneous wavelengths may bring more information about the optical properties and the refractive index of a particular component. In this regard, the refractive index could represent an important future parameter of biological tissue or pathological deposits such as drusen [39, 40]. Changes of such an index have already been reported after refractive surgery [41–44]. For that reason, the Hydra-OCT could contribute new insights into the state of tissue hydration [45], the behavior of multicellular tumor spheroids [46], age-related changes of the lens [47], characteristics of light transmission in Müller glial cells [48] and crystalline cones [49]. A previous report showed that different OCT devices may not be used interchangeably because higher choroidal thickness values were observed in SS-OCT compared to SD-OCT [50]. In this respect, the method presented in this manuscript is consistent since both wavelengths were executed using the identical spectral-domain technology and geometry in one single OCT device.

A limitation of the study was the small number of subjects. Another weakness would be that only one operator had carried out all measurements and no interoperator variation was evaluated. In addition, no reproducibility of the method was tested because this was not the aim of this first experiment. It is obvious that the grading of the images was simple, since the main goal of the study was to obtain data with regard to safety and feasibility. Another limitation of the study lies in the image grading of the two devices which was assessed by subjective descriptions only. In future studies it will be necessary to address these weaknesses.

In conclusion, the outcome of this study is that the dual wavelength OCT device described is comfortable, safe and provides similar images to an established device.

Acknowledgments

The authors would like to thank Heidelberg Engineering, Heidelberg, Germany, for their technical support.

Statement of Ethics

Approval from the local Swiss ethics committee (EKNZ: 2016-01435) and Swissmedic (reference No.: 10000317) and written informed consent were obtained from all subjects. The study was in adherence with the Declaration of Helsinki and in accordance with good clinical practice.

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Disclosure Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding Sources

The study was supported by a grant from Blueye Vision Tech GmbH, Luzern, Switzerland, Hirslanden Klinik, Luzern, Switzerland, B. Braun Medical AG, Sempach, Switzerland, Verein zur Förderung der Weiterbildung in der Augenheilkunde, the German Research Foundation (grant MU4279/2-1 to P.L.M.) and the Swiss National Science Foundation (grant 320030_146021). No sponsor or funding agency had any involvement in the design, collection, analysis and interpretation of the data, manuscript writing and the decision to submit the manuscript for publication.

Author Contributions

L.C., B.P., P.W.H., C.M., C.B., M.M., C.E., A.T., H.P.N.S., P.M.M.: conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing, original draft preparation, writing review and editing, visualization, project administration.

P.K., S.R., P.L.M., J.Z.V.: methodology, software, validation, formal analysis, data curation, writing, original draft preparation, writing review and editing.

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