Project Title

Development of automated tools for computing vitreous haze for assessment of intraocular inflammation

Project Lead and Members

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Organisation(s) Involved

Tan Tock Seng Hospital, Lee Kong Chian School of Medicine, Play On

Healthcare Family Group(s) Involved in this Project

Medical, Allied Health

Applicable Specialty or Discipline

Ophthalmology

Project Period

Start date: 01 Jul 2020

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Aims

- To develop a fully automated customized algorithm/ application to analyze Optical Coherence Tomography (OCT) scans and derive a robust marker for vitreous haze.
- To develop a qualitative algorithm for patient-reported outcome measure for assessing vitreous haze.

Background

The vitreous humour is a gelatinous body occupying the posterior segment, diffusely adherent to the retina. It acts as a metabolic repository for surrounding structures, with studies demonstrating close relationships between retinal changes and alterations in the vitreous' biochemistry (1, 2). Structurally, with a viscosity of two to four times that of water, the vitreous is composed of abundant cross-linked collagen fibres, hyaluronic acid, and glycosaminoglycans, helping to preserve the eye's shape (3, 4). But more importantly, the vitreous is a transparent media that enables light passage, playing an irreplaceable role in maintaining optimum visual acuity. Therefore, intraocular diseases that compromise the vitreous' integrity can lead to media opacity, resulting in significant visual deficits.

Uveitis is a group of diseases characterised by intraocular inflammation, with a myriad of bizarre causes ranging from infective to autoimmune (5). With the exception of anterior uveitis, inflammatory infiltrates and proteinaceous exudates build up within the vitreous regardless of the aetiology (5). On examination, the diseased vitreous assumes a 'hazy' appearance, which can be qualitatively classified as various grades of 'vitreous haze' (6, 7). The clarity of vitreous is related to disease activity, and corresponds to one's vision (8). Uveitis is therefore a major cause of blindness worldwide, with the highest prevalence in the working-age population, resulting in a significant socio-economic burden (9). Furthermore, the delivery of optimum care is constantly challenged by the absence of a reliable marker of disease activity (10, 11). However, with vitreous haze being described as the primary outcome measure for clinical trials and the proposed surrogate marker of disease activity, we ought to develop a system to accurately grade this promising parameter (8, 12-14).

Currently, there are two accepted systems, the National Eye Institute/Nussenblatt scale (NEI) and the Miami scale (6, 7). In principle, both rely on manual grading depending on the expert judgement made with reference to standard photographs, introducing the element of subjectivity. Individually, the NEI scale only has a moderate degree of inter-observer agreement. With just six levels of vitreous haze, the scale also

fails to provide a continuum of grading, successive grades do not have correspondingly proportionate/equal increments in disease severity. Furthermore, clinicians are often unable to discriminate low grades of vitreous haze using NEI. This system, though accepted by the US Food and Drug Administration, was also reported to have limited sensitivity (7, 15).

On the other hand, the Miami scale boasts nine different grades of vitreous haze, with graduated increments in severity corresponding to the logarithm of visual acuity. This was enabled by the usage of Bangerter foils to artificially obscure the fundus, thereby mimicking pathological states (7). The outcome of such was improved inter-observer agreement (7, 16, 17). But despite the convenience of grading at a glance, those qualitative systems are subjective and non-ideal for research, due to inter-observer variations, possible biases, and lack of repeatable quantifiers for statistical analysis. With that in mind, the development of quantitative parameters may bring about a positive impact in the research context, which may translate into improved patient care in the clinical setting.

With the advancements in ophthalmic imaging, Saito et al reported the utility of OCT in visualizing inflammatory cells in the vitreous, described to assume the appearance of punctate spots (18). Keane et al subsequently quantified vitreous haze by measuring signal strength with respect to retinal pigment epithelium (19, 20). The product, known as vitreous analysis software (VITAN), allowed both manual and automated computation. However, VITAN only demonstrated a moderate correlation with reader grade based on NEI (19).

In a recent proposal by Passaglia et al, the group developed an automated tool to grade vitreous haze based on fundus photographs (21). The method was reported to have a stronger agreement with reader grading as compared to VITAN. However, our group remains doubtful about its true accuracy. Firstly, the two-dimensional view of fundus photographs may be less ideal compared to multiple OCT B-scans. Secondly, mechanical obstruction by cataracts and small pupils in uveitis may further blur the

image. Lastly, the quality of the fundus image is dependent on the photographer's skill, introducing the element of operator dependence.

In short, the urgent need for a reliable quantitative parameter for vitreous haze remains unmet. Based on experience with ocular imaging, specifically OCT image analysis, our group has previously achieved success in quantifying choroidal vasculature by analysing and manipulating OCT scans, producing a biomarker named choroidal vascularity index (CVI) (22). Using similar principles of image binarization and automated segmentation, our group aims to develop a reliable quantitative parameter for vitreous haze based on OCT scans, termed vitreous haze index (VHI).

As the product is projected for clinical and research purposes, we hope to take a step further and engineer a fully automated algorithm that can be integrated into OCT machines. Such innovation will enable OCT machines to perform rapid analysis upon image acquisition. This improves efficiency, by enabling large sample analysis in a short period of time, and reduce the requirement for manpower. The machine-based analysis may also be more sensitive than reader grading, as the human eye has limited resolution. Furthermore, computer algorithms operate on a continuum, whereas manual grading is restricted to nine possible stages. Therefore, there can be finer stratification of disease severity, and detection of currently subclinical disease. With such, VHI algorithm will be useful in the clinical setting, for clinicians to obtain immediate information about the patient's intraocular inflammation status.

In the development of our alogrithm for VHI analysis, our group also envisions the usage of artificial intelligence (AI) and machine learning (ML) to perfect the algorithm. ML has been used in medical imaging for decades, particularly in computer-aided diagnostics (23, 24). The repeated fine-tuning of computerized software through ML will help ensure that the designed system is at least on par with a clinician's judgement, to perform intelligent predictions based on early data pool. Nichols et al even proposed that with progress in ML, the algorithms may eventually achieve and even surpass the level of a human expert in terms of information extraction (25).

In addition to the development of quantitative parameters (VHI) for vitreous haze, our group also envisages developing a qualitative panel for patients to report their symptoms of haziness/ blurred vision, which eventually can be further validated as a patient-reported outcome measure and important surrogate endpoints in patients with uveitis. In the Miami scale, the clinician's impression of patient's vitreous haze is obtained by comparing fundus findings with sample images (7). In our proposed qualitative panel of vitreous haze, there will be a series of sequentially blurred images for the patient to identify and match with their symptoms. Inclusion of an accurate qualitative component improves the robustness and comprehensiveness of our vitreous haze analysis, covering both the clinicians' and patients' perspectives. This qualitative component may be further validated by investigating for correlation with VHI and the existing Miami/NEI scales.

Methods

This is a cross-sectional and longitudinal study. 50 controls, 50 patients with uveitis and 20 patients with vitreous haemorrhage were recruited from Tan Tock Seng Hospital, National Healthcare Group Eye Institute and National Centre for Infectious Diseases eye clinic.

Data extraction (inclusive of images to support a medical diagnosis or condition) from research participant medical records will also be conducted -

1. Basic information, such as age at time of recruitment, race, etc.
2. Presence of systemic illness, such as hypertension, diabetes mellitus, etc.
3. Any other medical and/or eye condition, such as uveitis, vitreous haemorrhage, cataract, etc.
4. Ocular parameters, such as visual acuity, intraocular pressures, refractive error, etc.
5. Blood pressure and other relevant health information.

Data collected will be de-identified so that no personally identifying information can be found on the research data and data collected will be stored for future research only if participants gave informed consent.

OCT image processing:

Proposed fully automated algorithm:

Computation of VHI consists of two major steps:

i. Delineation and computation of region of interest (ROI) i.e. the vitreous
ii. Vitreous haze analysis

Results

The investigator has previously used the VITAN alogrithm from Keane et al but numerous challenges were encountered:

1. Inability to segment the entire vitreous, providing only a representative segment of the vitreous.
2. Inability to differentiate between old vitreous haze and active vitreous inflammation.
3. Poor correlation with objective vitreous haze grading by the examiner

Based on the success of choroidal vascularity index, an established choroidal biomarker, our group aims to apply the similar principles of image binarization to analyse the vitreous on OCT scans. Hyperreflective spots in the vitreous, after the reduction/removal of excess noise, are postulated to represent the vitreous haze seen through the ophthalmoscope/fundus photograph. Based on such, we propose VHI as a quantitative parameter to indicate vitreous haze.

Lessons Learnt

PAll tests for the respective subject groups will be carried out as standard clinical tests and not research tests, depending on the judgment of the primary clinician.

Slit-lamp Biomicroscopy: A non-invasive examination that uses a slit lamp to shine a thin sheet of light into the eye. There are no known or expected side effects.

Fundus Photograph: A non-invasive test that captures colour photographs of the retina. There are no known or expected side effects.

Optical Coherence Tomography (OCT) Imaging: Non-invasive OCT imaging using FDA approved OCT. This should cause no discomfort. Subjects will be seated in front of a device with chin rested and will be asked to look at a target while the apparatus captures the image of the back of eye. More detailed instructions will be given at the time the test is carried out. These tests will take only a few minutes in total. There are no known or expected side effects.

VA, IOP, refraction test: Measurement of eye pressure can rarely cause mild eye discomfort or corneal abrasions following eye pressure measurements. Allergy to the preservative in the anaesthetic eye drop instilled prior to eye pressure measurement can also rarely occur. This may cause itchiness or redness of the eye. The eye drop used to dilate the pupils can cause temporary blurring of vision for a few hours. There are no known or expected side effects.

There are no risks involved with any of the research tests except that some participants may feel a bit uncomfortable with the test due to excessive use of light source.

Confidentiality will be maintained as per normal between study subjects and members of the study team.

Conclusion

If biomarkers of disease activity, VHI can allow the clinician to make a more accurate decision on the duration of therapy, thus reducing morbidity by decreasing the chance of under-treatment that can lead to disease recurrence and the chance of over-treatment that is associated with immunosuppression side effects.

Additional Information

We will plan to move it to POV state, also we are going to validate this toll through prospective study. We are also intending to license this product to a commercial vendor. We are applying for other NMRC grants. We are intending to use it at NHGEI, TTSH.

Project Category

Technology

MedTech, Product Development, Commercialisation, Proof of Value, Evaluation Criteria

Applied/ Translational Research

Quantitative Research

Keywords

Vitreous, Software, Binarisation

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Inter-rater Agreement for OCT-derived Vitreous Dots Index (VDI) in Uveitis and Healthy Populations; Insights from OCTOMERIA Study

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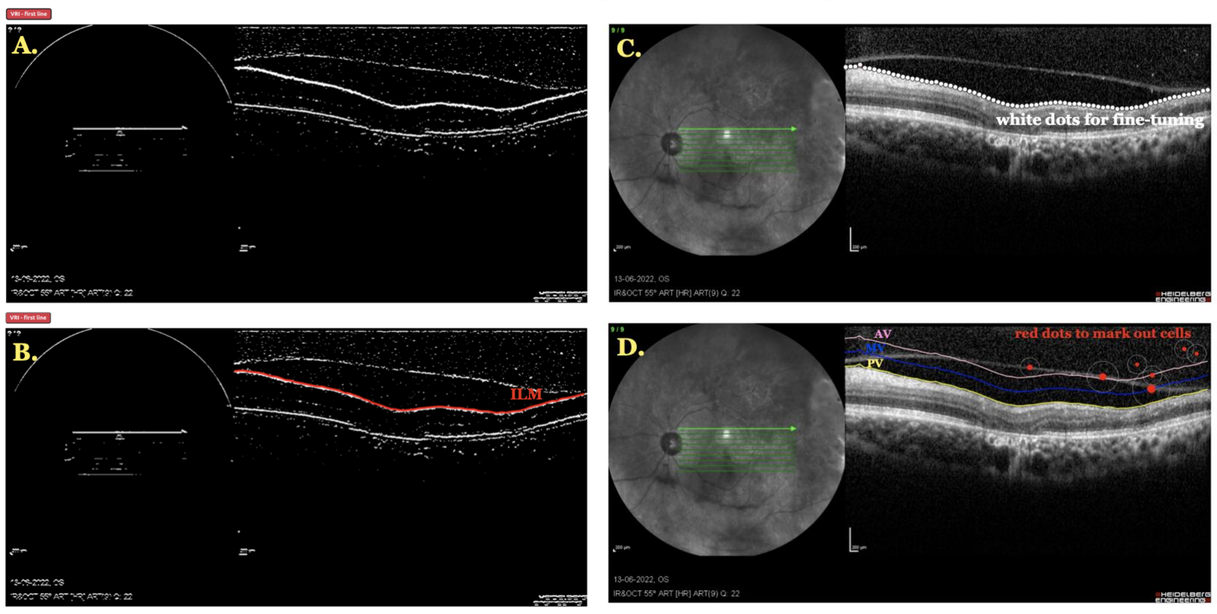
Introduction

Uveitis encompasses a heterogenous group of intraocular inflammatory diseases[1]. It is difficult to assess clinically due to its subjective and variable grading[1,2]. We developed a quantitative biomarker and assessed its reproducibility in severity grading of vitreous inflammation. In this study, we aim to assess inter-rater agreement on semi-automatically calculated vitreous dots indices (VDI) derived from optical coherence tomography (OCT) scans.

Methods

We recruited patients presenting to Tan Tock Seng Hospital (TTSH) and National Centre for Infectious Disease (NCID) eye clinic, with and without ocular inflammatory disease as subjects for the uveitis and control groups. OCT scans of the studied eyes (one per subject, either left or right) were taken. A total of 1036 OCT scans from 34 eyes (23 healthy, 11 uveitis) were processed using our semiautomated software (OCTOMERIA Study). We used a vector tracing algorithm to determine the internal limiting membrane (ILM), to delineate the vitreous as our region of interest (ROI). The vitreous was automatically segmented into 3 zones (Zone 1 : 100 microns from vitreo-retinal interface (VRI) , Zone 2 : 100 to 200 microns from VRI, Zone 3 : more than 200 microns from VRI) and used as references for vitreous cell locations. TV was the total vitreous area.

Figure 1. flow chart summarising the steps for image segmentation.



Hyperreflective, round dots representing vitreous cells were manually identified on OCT images by clicking on the image and placing a red dot. VDI was recorded as the number of dots (VDI-N) and area of dots (VDI-A) within each vitreous compartment to indicate levels of vitreous inflammation. We compared results obtained by two trained independent graders using intraclass correlation coefficient (ICC).

Results

In the control group, ICC between graders for VDI-N in TV, Zone 1, Zone 2, and Zone 3 were r=0.91 (0.90 to 0.92, p<0.001), r=0.9 (0.89 to 0.92, p<0.001), r=0.79 (0.76 to 0.82, p<0.001), and r=0.37 (0.31 to 0.43, p<0.001), respectively.

In the uveitis group, ICC between graders for VDI-N in TV, Zone 1, Zone 2, and Zone 3 were r=0.92 (0.90 to 0.94, p<0.001), r=0.92 (0.90 to 0.93, p<0.001), r=0.84 (0.80 to 0.87, p<0.001), and r=1.00 (1.00 to 1.00, p<0.001) respectively.

ICC for VDI-A markers are presented in Figure 2.

Figure 2. Inter-grader reliability assessment of VDI markers in 34 study subjects.

		Control Group			Uveitis Group		
		ICC (95% CI)	p-value	mean difference (95% LOA)	ICC (95% CI)	p-value	mean difference (95% LOA)
Number of Dots (VDI-N)	Zone 3	0.37 (0.31 to 0.43)	<0.001	-0.00 (-0.24 to 0.23)	1.00 (1.00 to 1.00)	<0.001	0.00 (0.00 to 0.00)
	Zone 2	0.79 (0.76 to 0.82)		-0.03 (-0.75 to 0.68)	0.84 (0.80 to 0.87)		0.01 (-0.47 to 0.49)
	Zone 1	0.91 (0.89 to 0.92)		0.14 (-2.14 to 2.42)	0.92 (0.90 to 0.93)		0.25 (-1.63 to 2.13)
	TV	0.91 (0.90 to 0.92)		0.11 (-2.30 to 2.51)	0.92 (0.90 to 0.94)		0.26 (-1.77 to 2.30)
Area of Dots (VDI-A)	Zone 3	0.02 (-0.06 to 0.09)		-0.01 (-0.50 to 0.47) x10^{-5}	1.00 (1.00 to 1.00)		0.00 (0.00 to 0.00)
	Zone 2	0.89 (0.88 to 0.91)		-0.02 (-0.52 to 0.47) x10^{-5}	0.79 (0.75 to 0.83)		-0.10 (-4.57 to 4.38) x10^{-7}
	Zone 1	0.46 (0.40 to 0.52)		-0.25 (-3.05 to 2.56) x10^{-5}	0.53 (0.44 to 0.60)		-0.30 (-3.68 to 3.07) x10^{-5}
	TV	0.52 (0.47 to 0.58)		-0.28 (-3.18 to 2.61) x10^{-5}	0.53 (0.45 to 0.60)		-0.30 (-3.67 to 3.07) x10^{-5}

VDI-N, vitreous dot index in terms of number of dots; VDI-A, vitreous dot index in terms of area of dots; Zone 3, anterior vitreous; Zone 2, middle vitreous; Zone 1, posterior vitreous; TV, total vitreous; ICC, intraclass correlation coefficient; CI, confidence interval; LOA, limits of agreement.

Figure 3a. Bland Altman Plots of VDI-N in Control Subjects.

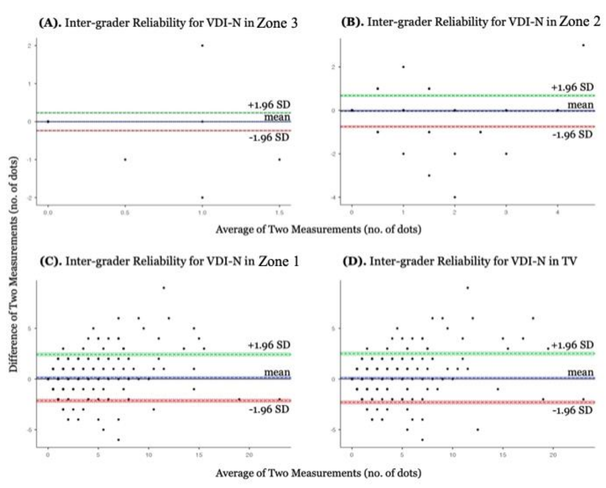
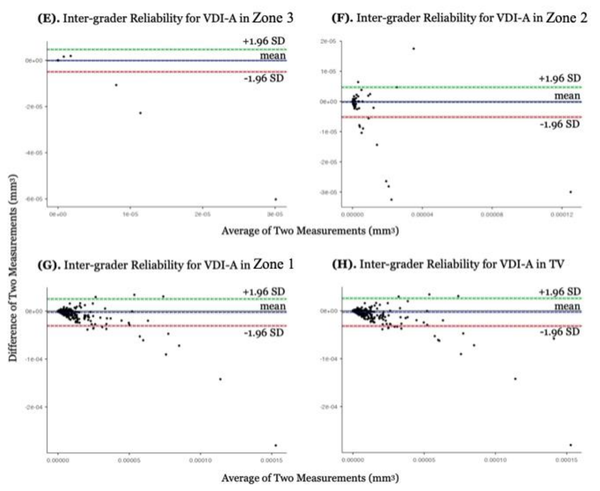


Figure 3b. Bland Altman Plots of VDI-A for Control Subjects.



Conclusion

In general, correlation for VDI-N values were excellent-good in TV, Zone 1, and Zone 2 for both uveitis and control groups. The inter-rater agreement for VDI-A values between graders were highly variable, depending on the area of segmentation.

Our preliminary results suggests feasibility in using VDI as a reproducible, quantifiable and objective marker of vitreous inflammation in uveitis. Further studies should focus on assessing VDI markers in relation to disease severity with larger sample sizes.

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