

DME-OSA Study

PROTOCOL: DME-OSA

PRIMARY INVESTIGATOR: Dr. Sohel Somani

CO-INVESTIGATOR: Dr. Alan Kosaric, Dr. M.R. Goolam Hussain

PROTOCOL TITLE: Examining the relationship between Diabetic Macular Edema and Obstructive Sleep Apnea: prevalence, association and impact.

SHORT TITLE: DME-OSA study

INTRODUCTION

Study Rationale

Obstructive sleep apnea (OSA) is a well-studied disease affecting millions of North Americans. OSA causes intermittent episodes of hypoxemia which may cause hypertension in some patients. Increased severity of OSA is linked with an increased chance of developing coronary artery disease, heart failure, arrhythmias, and stroke, which may lead to sudden death. OSA can also cause daytime fatigue and random onset of sleep, which can cause serious harm to the patient if engaging in an activity requiring a high level of mental focus (i.e. driving). OSA can also impact a patient's response to medications and surgery; general anesthesia can worsen OSA due to its impact on the upper airway increasing complications post-surgery. Most OSA patients are undiagnosed; many do not consider snoring or other symptoms as cause for concern, adjusting to maintain an adequate lifestyle. However, undiagnosed OSA can lead to severe comorbidities and possibly the demise of the patient.

OSA has been found to affect up to 86% of type 2 diabetic patients [1, 2]. Chronic intermittent hypoxia (CIH) is a feature of OSA that has shown to increase insulin resistance [3]. A causal link between OSA and diabetes has yet to be established; however, the prevalence of diabetes in OSA patients is significantly higher (15%) compared to the general population (3%)[4]. In essence, the relationship has been shown to be bidirectional (i.e. OSA patients are more likely to develop diabetes and diabetic patients are more likely to develop OSA than the general population).

Based on this relationship, researchers sought out to identify whether a correlation exists between microvascular complications of diabetes, such as diabetic retinopathy (DR) and OSA. A Japanese study identified a 29% and 48% prevalence of OSA among patients with non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) respectively; the difference in prevalence being significant[5]. The authors suggest a potential relationship between OSA and the development of PDR. In another study at Oxford, West et al (2010) identified a 24% prevalence of OSA in men with Type II diabetes, indicating that OSA and HbA_{1c} were the only significant predictors of retinopathy[6]. However, another study describes the relationship between DR and OSA as statistically insignificant[7].

A review of the literature has shown there to be limited studies looking at the relationship between OSA and diabetic maculopathy[8]. One study identified a 65% prevalence of OSA among patients with clinically significant macular edema (CSME)[9]. However, the authors did

not find a statistical significance between the severity of maculopathy and the severity of OSA. Another study identified no difference between retinopathy in patients with or without OSA (39% vs. 38%) but did find an association between maculopathy in patients with OSA compared to those without (22% vs. 13%) but this was not statistically significant[7]. The results of both these studies are limited by the use of a home sleep studies rather than an overnight sleep study. Treating OSA with continuous positive airway pressure (CPAP) has shown to improve visual acuity in DME patients but no changes in macular thickness was observed[10].

The current literature lacks a thorough analysis of the relationship of DME and OSA. Of the few studies that assess macular edema and OSA, home sleep studies were conducted. In this study protocol, we aim to have patients thoroughly evaluated in an overnight sleep lab monitored by a sleep specialist. Furthermore, appropriate interventions will be carried out if positive OSA is identified-

STUDY OBJECTIVES

Our study aims to answer more definitively the relationship between OSA and DME on three levels:

1. What is the prevalence and correlation of OSA in a DME population?

We hypothesize a relationship does exist based on previous studies of DME and OSA (65% prevalence of OSA among DME patients). However, this study diagnosed OSA using a home sleep study, which is not considered to be a true gold standard test in sleep medicine research. We aim to identify the presence of OSA using the gold standard testing of an overnight sleep study to determine the prevalence of OSA in the DME population. Further, we will attempt to determine if there is a correlation of OSA by comparing it to non-DME patients who have NPDR.

2. Is there an association of severity between OSA and DME?

The second clinical question entails whether the severity of OSA is correlated with the severity of DME. The mechanism of OSA action on diabetic microvascular complications may involve increased inflammatory responses and oxidative stress pathways such as increased advanced glycation end products[11, 12]. Thus, we hypothesize that the increased severity of OSA will be positively correlated with increased severity of DME. By comparing the gold standard metric of severity index of OSA (Apnea-hypopnea index) to DME metrics (LogMAR Snellen vision and CRT) at the baseline of both disease diagnoses, we can determine severity association.

3. Is there any impact on OSA treatment (i.e. CPAP) on DME treatment?

Only one study has attempted to identify if OSA treatment can enhance DME outcomes. Mason et al (2012) found a significant improvement of visual acuity among OSA treatment patients but their macular thickness was not significantly different. We aim to further

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explore this relationship by comparing the results of DME treatment 1 year following CPAP initiation. The specific metrics of DME treatment (Vision, CRT, number of injections) will be compared to pre-CPAP data to determine what the impact of CPAP was (if any) on DME treatment metrics. Further, we aim to compare the one-year post-CPAP DME treatment metrics against one-year non-CPAP/non-OSA patients to determine the relative impact against a control group.

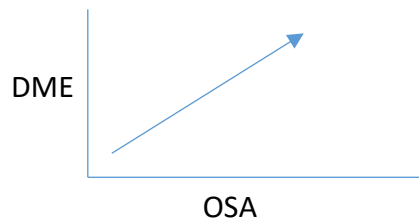
We hypothesize that CPAP users demonstrate an improvement on Vision and CRT metrics compared to prior to initiation of CPAP. We further hypothesis that CPAP users and non-CPAP users have equivalent visual acuity, CRT, and number of injections due to the neutralization effect (i.e. OSA neutralized by CPAP).

In summary:

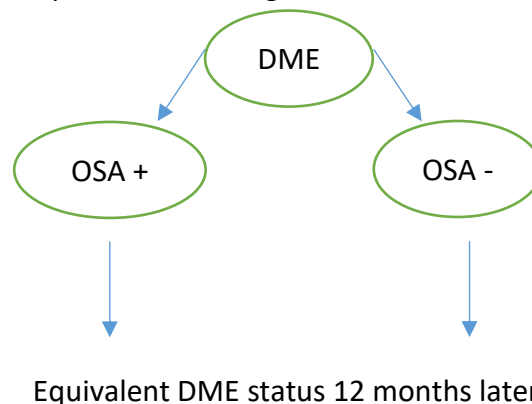
Question 1: Is there a correlation between DME and OSA?

	DME +	DME - / NPDR +
OSA +		
OSA -		

Question 2: Is there a relationship between the severity of DME (CRT and vision) and OSA (AHI index)?



Question 3: Does treating OSA result in improving DME metrics, and does it neutralize the outcomes at 1 year compared to OSA negatives.



INVESTIGATIONAL PLAN

Study Design

A 12 month, non-randomized, controlled, prospective study evaluating the relationship between diabetic macular edema (DME) and obstructive sleep apnea (OSA). Investigational sites will have Ethics Review Board approval prior to enrolling patients.

All subjects who meet eligibility criteria will be consecutively offered enrollment into the study until the study has fulfilled all enrollment requirements, or terminated by the Primary Investigator. The study will be initiated upon Ethics review and approval.

PATIENT SELECTION

Key Inclusion Criteria

- 18 years of age or greater
- Ability to understand and provide written consent
- Type II diabetes patients and evidence of Diabetic Retinopathy
- Patients with and without DME
- Able and willing to comply with all treatment and follow-up procedures

Key Exclusion Criteria

- Contraindications to Eylea including: stroke within the past month, ocular or periocular infection, active intraocular inflammation, hypersensitivity to Eylea and/or its excipients.
- Contraindication to CPAP including: severe bullous lung disease, pneumothorax, pathologically low blood pressure, dehydration, cerebrospinal fluid leak, recent cranial surgery, or trauma
- Any other types of retinal diseases such as retinal detachment
- Any other types of macular disease such as age-related macular degeneration
- Mental capacity to comply is impaired (i.e. dementia)
- Pregnant or breastfeeding women
- Participation in any drug or device clinical investigation within 30 days prior to entry into the study

Subject Enrollment

The subject must satisfy all eligibility criteria to enroll. The subject is considered enrolled in the study at the time the first anti-VEGF injection is administered.

Subject Completion

The subject has completed the entire study after 12 months of receiving routine injections to the study eye and has initiated CPAP treatment, if applicable, for at least 3 months.

Subject Withdrawal

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A subject may discontinue from the study prior to the final study visit due to voluntary withdrawal or death. Prior to discontinuing a subject who voluntarily withdraws, every effort should be made to contact the subject, schedule a final study visit, and obtain as much follow-up data as possible. Discontinued subjects who withdraw consent should be followed outside of the study protocol according to the Investigator's normal standard of care. The Investigator may withdraw a patient for rescheduling appointments that prevent them from following the protocol's injection schedule.

Premature patient withdrawal from the study

Patients will be withdrawn from the study under the following circumstance:

- Withdrawal of study informed consent
- Patient exhibits one or more contraindications to Eylea or CPAP as described in the exclusion criteria or develops an unexpected AE with respect to the study treatment (either Eylea or CPAP if applicable)
- Worsening of diabetic macular edema despite optimal Eylea dosing (requiring a second line rescue medication or procedure)
- Patient develops a new retinal or macular disease along the course of the study
- Patient becomes pregnant or begins breastfeeding
- Patient's mental status and capacity becomes significantly altered (i.e. develops dementia)
- Patient switches treatments
- Patient non-compliance defined as missing at least 2 consecutive study visits

If premature withdrawal occurs for the reasons described above, the investigator should make every effort to record the primary reason for a patient's premature withdrawal from the study on the Study Completion CRM.

Lost to Follow-up

Subjects who do not return for their routine injections or must reschedule due to personal reasons may be considered lost to follow-up. All follow-up attempts will be documented and kept with the subject's source documentation.

PLANNED STUDY PERIOD AND DURATION OF TREATMENT

The duration of the study, including the time to recruit all subjects, will be up to 12 months. Eligible subjects who are enrolled in the study will be seen for up to 12 months.

Early Study Termination

If during the study, the primary investigator determines that the study should be stopped prematurely, the study will be terminated or suspended and appropriate notification will be given to the investigator(s) and patients.

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PROTOCOL

Design

Subjects eligible for the inclusion in the study will be grouped based on their diagnosis: DME & OSA positive, DME positive only, OSA positive only, and DME & OSA negative.

All DME positive patients (irrespective of OSA status) will receive the standard of care treatment with anti-VEGF using Eylea in a standardized treat and extend protocol.

Patients above the age of 65, the Eylea product is covered under the public health plan (ODB). Patients under the age of 65, the Eylea product will be provided by the patient's private plan. In the absence of such a plan, the Eylea product will be provided at no cost to the patient. CPAP machines will need to be purchased by the patient if they are diagnosed with sleep apnea and their private plans do not cover it. All DME negative patients will not be receiving Eylea. All DME positive patients will receive Eylea until resolution of DME. This is not a drug trial, hence no placebo or randomization issues that affect accountability is applicable.

All patients (irrespective of DME status) will be sent to a sleep lab to identify OSA status. OSA positive patients will be provided the standard of care (i.e. CPAP) treatment. CPAP machines will be prescribed and the patient will be responsible to purchase the machine using provincial and/or private insurance, or personal funds.

Study Size

All groups to include 150 patients total (i.e. 75 DME positive, 75 DME negative)

Participating Sites

The clinical trial will be conducted at up to 3 investigative sites located in Canada. The study will be conducted by Investigators who are determined by the Primary Investigator to be suitably qualified by training and experience to conduct this study in compliance with all applicable good clinical practices (GCPs). Each investigative site (except the sleep lab) will attempt to enroll a minimum of 10 subjects. In the event that selected sites do not meet full enrollment, the Primary Investigator may decide to increase enrollment as needed at other currently active sites and/or additional site(s) may be added to satisfy the enrollment requirements of the study. The primary Investigator will monitor other sites through monthly review of all CRMs to ensure proper documentation (consent, CRM, etc) and protocol adherence.

Study methods

Subjects who meet eligibility criteria will be seen according to the following schedule (unless discontinued or lost to follow-up) and must adhere to the following schedule:

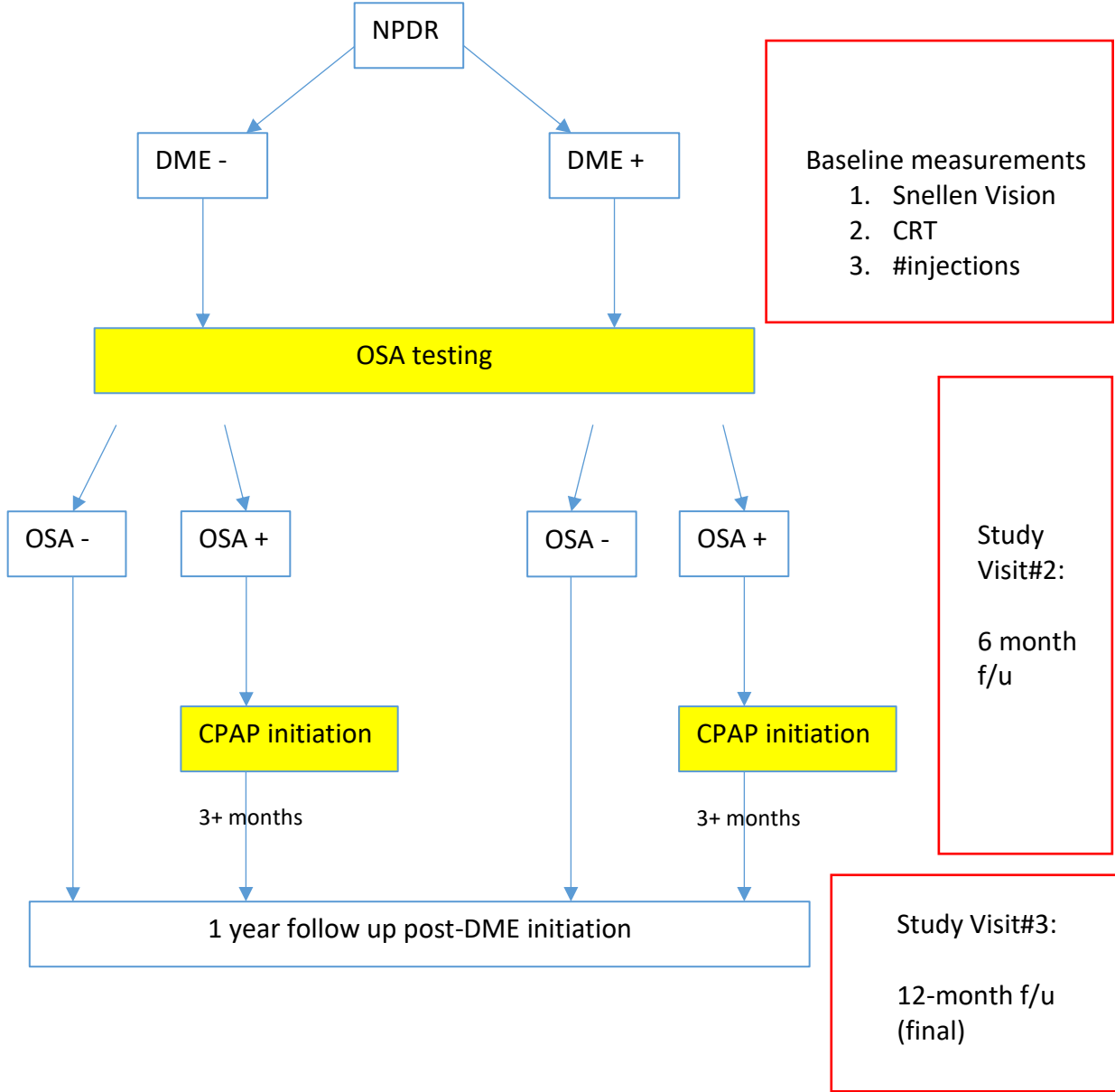
Visit 1: Baseline DME Treatment or NPDR diagnosis (if not DME)

Visit 2: Diagnosis of OSA – Overnight sleep study + consult

Visit 3: 6-month visit post DME initial treatment

Visit 4: 12-month visit post DME initial treatment in the OSA- group and at least 3 months post CPAP initiation in the OSA+ group

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Table 1

	Visit 1	Visit 2 Dx of OSA		Visit 3	Visit 4			
	Baseline DME treatment or NPDR dx (if not DME)	Diagnostic	CPAP	6-month f/u	12-month f/u			
Vision (Snellen BCVA)		N/A						
CRT (OCT Macula)								
Total injections to date								
Fundus exam - DR score								
Baseline Ocular Metrics*						N/A	N/A	
ESS	N/A			N/A	N/A			
SSS			N/A					
AHI								
REM sleep								
Awakenings								
Mean O2 SAT								
Min O2 SAT			N/A					
OAI								
ODI								
Compliance			N/A					
HbA1c								
Baseline Sleep Metrics*								
Visits to ophthalmologist (blue)								
Visits to sleep specialist (green)								
*Baseline ocular and sleep metrics detailed in Table 2								

BCVA → best-corrected visual acuity; CRT → Central Retinal Thickness; OCT → Optical Coherence Tomography
 ESS → Epworth Sleepiness Scale; SSS → Stanford Sleepiness Scale; AHI → Apnea-hypopnea index; OAI → Overall arousal index; ODI → Oxygen desaturation index

Table 2

	Visit 1	Visit 2 Dx of OSA
	Baseline DME treatment or NPDR dx (if not DME)	Diagnostic
RAPD		N/A
AR		
Pachymetry (CCT)		
IOP		
PENTACAM topography		
Cornea SPK		
Upper eyelid papillary conjunctivitis		
Eyelid elasticity score		
OCT RNFL		
VF		
Vitals: BP, HR, O2	N/A	
Ethnicity		
Age		
Sex		
Neck circumference		
Height		
Weight		
BMI		

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Duration of diabetes		
Past Medical History		
Past Surgical History		
Medications		
Waist Circumference		
Smoking		
Alcohol		

RAPD → relative afferent pupillary defect; AR → autorefractor; RNFL → retinal nerve fiber layer; VF → Visual field; IOP → intraocular pressure; CCT → central corneal thickness;; SPK → superficial punctate keratitis

During each visit, the intraocular pressure and perfusion of the optic nerve head will be monitored for patient safety.

Visual acuity testing is a primary marker of efficacy and subject safety, as any decline in this parameter triggers a clinical evaluation for cause. During each study visit, patients will also have an opportunity to report of any safety issues.

Table 3: DME positive patients will receive a minimum of 6 injections with the first five occurring at 1-month intervals and the sixth occurring two months after the fifth. Further injections will be provided at the discretion of the ophthalmologist in according to the treat and extend protocol of Eylea. Data for Visits 1 and 4 in Table 1 will be collected at the first and sixth injections whereas the other injection visits will be treated as regular office visits and not study visits.

DME EYLEA TREATMENT

INJECTION 1	Collect data
INJECTION 2	n/a
INJECTION 3	n/a
INJECTION 4	n/a
INJECTION 5	n/a
INJECTION 6	Collect data

ADVERSE EVENTS

Throughout the course of the study, all efforts will be made to remain alert to possible AEs. If an AE occurs, the first concern will be the safety of the subject and appropriate medical intervention will be made. All ocular AEs that occur in the study eye and all systemic AEs (both ocular and non-ocular) will be collected. Non-serious non-ocular AEs will not be reported. The collection of AEs begins at the time the subject is enrolled into the study.

Common adverse events to Eylea to be reported include: conjunctival hemorrhage, eye pain, cataract, and vitreous floaters. Adverse events to CPAP may include: drying of the nose, mouth, or throat, nosebleed, bloating, ear or sinus discomfort, eye irritation, or skin rashes.

Serious Unexpected Adverse Drug Reaction Reporting

During the course of a clinical trial, the sponsor shall inform the Minister of any serious unexpected adverse drug reaction in respect of the drug that has occurred inside or outside Canada as follows:

- (a) if it is neither fatal nor life threatening, within 15 days after becoming aware of the information; and
- (b) if it is fatal or life threatening, within seven days after becoming aware of the information.

The sponsor shall, within eight days after having informed the Minister under paragraph (1)(b), submit to the Minister a complete report in respect of that information that includes an assessment of the importance and implication of any findings made.

The AE's that will be reported are those that are NOT associated or described in the product monograph - as these will truly be "unexpected" in nature.

To ensure patient safety, every SAE (serious adverse event), regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last injection of Eylea) must be reported to Bayer within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30-day period should only be reported to Bayer if the investigator suspects causal relationship to Eylea.

Recent episodes, complications, or progression of initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse event Report Form. The investigator must assess the relationship of any SAE to Eylea, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the local Bayer Druga Safety and Epidemiology Department. The telephone and telecopy number of the contact persons in the local department of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

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Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the local product label or package insert (new occurrence) and is thought to be related to Eylea, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting.

Any device problem reports (as described in Health Canada Guidance Document for Mandatory Problem Reporting for Medical Devices) related to the CPAP device will be reported promptly to the manufacturer.

STATISTICAL METHODS

Primary Clinical Endpoints

- Presence of DME and OSA
- DME: Snellen Visual Acuity
- OSA: Apnea-hypopnea index

Primary Safety Endpoints

- Incidence of cumulative adverse events (AEs; evaluated at all visits)

Secondary Clinical Endpoints

- DME: CRT, # of injections
- OSA: compliance

Tertiary Clinical Endpoint

- The International Clinical Disease Severity Scale for Diabetic Retinopathy [13] based on clinical exam or colour fundus photography:
 - No DR
 - Mild Retinopathy
 - Moderate Retinopathy
 - Severe Retinopathy
- Hemoglobin A1c

Randomization

Randomization is not applicable to this study.

Sample size

150 patients – 75 DME positive, 75 DME negative

Estimates based off 65% prevalence in DME+ patients and 29% in NPDR+.

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	DME +	DME -/NPDR +
OSA +	48	21
OSA -	27	54

Statistical analysis

Assuming the prevalence of OSA as 65% in DME+ patients and 29% in DME-/NPDR+, a sample size of 75 patients in both DME+ and DME- group provides >99% power to detect correlations between DME and OSA (Research Question 1), with a two sided test controlling type I error as 0.05. A slight over power here due to the considerations of research Question 3 in comparing DME metrics (i.e., Snellen VA for sample size calculation) between OSA+ (CPAP+) and OSA- (CPAP-) patients: assuming a SD of 2 lines in Snellen VA (based on extrapolation from the RISE/RIDE paper), and the same prevalence as given above (65% and 29%), a sample size of 75 patients in both DME+ and DME- groups would provide 85% power to detect a difference in Snellen VA of 1 line between OSA+ and OSA- patients, in a 2 sided test with type I error controlled as 0.05. The research Question 2 is more exploratory and not considered in the sample size calculation.

APPENDIX

Description of procedures:

Vision (Snellen BCVA): measuring visual acuity using a typical Snellen chart providing vision as 20/100, 20/50, etc. This value is converted to a logarithmic scale (i.e. LogMAR BCVA)

Central Retinal Thickness (CRT): Central retinal thickness is measured using an optical coherence tomography to ensure no damage to retinal occurs

Fundus exam: assessment of the retina, optic nerve head, blood vessels, and other features of the eye.

Relative afferent pupillary defect (RAPD): a condition in which pupils respond differently to light stimuli shone in one eye at a time due to unilateral or asymmetrical disease of the retina or optic nerve

Autorefractor (AR): provides an objective measurement of a person's refractive error and prescription for glasses or contact lenses

Retinal Nerve Fiber Layer (RNFL): evaluating the retinal nerve fiber layer is essential in understanding the patient's current ocular diseases and potential future occurrences.

Visual Field (VF): entire area that the patient is able to see when their eyes are fixed in one position

Intraocular Pressure (IOP): fluid pressure inside the eye

Central Corneal Thickness (CCT): measures the thickness of the cornea using corneal pachymetry

Superficial Punctate Keratitis (SPK): evaluating presence or absence of SPK, an eye disorder caused by death of small groups of cells on the surface of the cornea

Epsworth Sleepiness Scale (ESS): measures a person's general level of daytime sleepiness

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Stanford Sleepiness Scale (SSS): measures how alert a person is feeling in the moment

Apnea-Hypopnea index (AHI): index used to indicate the severity of sleep apnea

Overall arousal index (OAI): an intrusion or disturbance in your sleep pattern as measured by EEG brain wave activity

Oxygen desaturation index (ODI): number of times per hour of sleep that the blood's oxygen level drop by a certain degree from baseline

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