Examining disparity driven vergence as a potential diagnostic test for mild traumatic brain injury (mTBI)

NCT Number NCT03529799

1) **Protocol Title**

Examining disparity driven vergence as a potential diagnostic test for mild traumatic brain injury (mTBI)

2) **IRB Review History***

None.

3) **Objectives***

Specific Aim 1 (SA1): Determine the validity and safety of disparity driven vergence testing with a portable goggle system using a pseudorandom ternary sequence of frequencies on a group of normal subjects.

Specific Aim 2 (SA2): Determine the vergence testing control values using a portable goggle system using a pseudorandom ternary sequence of frequencies on a group of normal subjects.

Specific Aim 3 (SA3): Determine the vergence testing values with a portable goggle system using a pseudorandom ternary sequence of frequencies on a group of subjects with history of mild traumatic brain injury and compare this to values in normal subjects.

4) **Background**

Vergence eye movements for focusing on objects include either convergence, the coordinated movement of both eyes towards the midline, or divergence, the coordination movement of both eyes towards the periphery. These eye movements are thought to be controlled by complex neurophysiological mechanisms that can be susceptible to damage by traumatic brain injury. Known involved areas in vergence include the oculomotor nucleus, cerebellum, and visual association cortex (Conn 2016), all of which can sustain damage during head trauma.

Modern balance function assessment includes electronystagmography and more recently, videonystagmography (ENG/VNG) to assess vertigo, dizziness, and imbalance. Additionally, vestibular-evoked myogenic potentials (VEMP), rotational testing, and computerized dynamic posturography (CDP) are very useful in evaluating multi-sensory integration of vision, somatosensory, and vestibular system function. VNG records eye movements using digital video image technology employing infrared illumination to determine eye position. The use of VNG enables simultaneous subjective observation of eye movements together with objective data collection and analysis of eye movement waveforms via computer algorithms (Kang 2015). More recently vestibular function has been tested in rotational chair devices. These devices utilize VNG goggles and perform many of the same tests done in a traditional VNG test but adds tests that involve moving the body (and with the body the head) through a variety of motion paradigms. Eye response to these body/head accelerations are recorded and abnormalities can be plotted against established norms. This technology is useful but involves a large and expensive piece of equipment in a dedicated vestibular lab. As a result, portable devices have been developed that perform many of the same functions that the chair performs. Head to head comparisons between rotational chair testing and portable vestibulo-ocular reflex gain and phase testing have shown consistent results between modalities (Goebel 1995). Portable vestibular testing has thus become a reality, allowing physicians

and audiologists the ability to test subjects outside of the typical clinical setting and in a variety of environments and conditions.

As such portable devices arise and become available to practitioners, their safety, validity, and efficacy must be determined. The portable goggle system, IPAS goggles (Neuro-kinectics, Inc., Pittsburgh, PA), have been developed to measure vestibular function and can be used for vergence testing. Current tests of binocular disparity driven vergence examine only one frequency (0.1 Hz) and tests at that single frequency may provide only limited information in the diagnosis and follow-up of mTBI patients. A greater number of frequencies can provide a spectrum of values that may help with this assessment. As testing all of the possible frequencies is not

feasible, we propose a pseudorandom ternary sequence approach to frequency distribution during disparity driven vergence to allow rapid analysis over a wide range of frequencies. Essentially, a pseudorandom frequency distribution can help extrapolate data to a larger frequency data set. We will also be evaluating the safety and side effect profile of using the goggles using a medical symptom questionnaire.

5) **Inclusion and Exclusion Criteria**

Inclusion:

- Aged 18 or older
- Both females and males

Exclusion:

- Central processing disorder
- Impaired vision without corrective lenses (max 20/60 uncorrected)
- Moderate to severe hearing loss (>55dB PTA, <50% word identification)
- Vestibular disorder except for patients recruited for SA3
- History of ear surgery other than myringotomy with or without tube placement
- Pregnant women
- Prisoners
- Adults unable to consent

6) **Number of Subjects**
60 subjects – 30 normal controls (no mTBI), 30 patients with mTBI.

7) **Recruitment Methods**
Normal subjects will be recruited from a pool of patients from a population who are unaffiliated or affiliated with University of Miami and meet inclusion criteria and not excluded by exclusion criteria. The faculty and students of any University of Miami School will be recruited through advertising in e-mails. Emails will be sent to staff and faculty associated with the UM Clinical Research Building (CRB) that have their emails stored in the UM Outlook server. Subjects will not be paid to participate. Students and staff will be assured that their participation will have no effect on their school performance or grades.

8) mTBI patients will be recruited by convenience from a pool of patients with history of mTBI and no prior vestibular disorders that present to the UM CRB Otology Clinic of Dr. Hoffer (SA3)". The determination of their fitness for participation will be made during Dr. Hoffer's clinical history and physical by asking about the history of the head injury and past medical history.

9) **Study Timelines**
Vestibular tests will take 15 minutes.

10) **Study Endpoints**
Each participant's study will be completed when they have completed the vergence testing and other vestibular tests. At that point, the data will be de- identified.

11) **Procedures Involved**
The study will be conducted in 2 phases in which each phase comprises of thirty participants.
In the first phase, thirty participants without mTBI who meet the inclusion criteria and are not excluded will be chosen to participate. Participants will sign an informed consent document and undergo 1 session of vergence testing, along with a series of vestibular tests. After this testing, the data will be de-identified and will only be labeled with sex and age of patient.
In the second phase, thirty participants with mTBI who meet inclusion criteria and are not excluded will be chosen to participate. Participants will sign an informed consent document and undergo 1 session of vergence testing, along with a series of vestibular tests. After this testing the data will be de-identified and will only be labeled with sex and age of patient.
After the session, patients will be given a medical symptom/toxicity questionnaire (MSQ) to evaluate for any side effects.and the SCAT-5 questionnaire, which will evaluate their current symptoms.

For each vestibular test and data to be obtained, see table below:

Test	Activity	Outcome OR Ordinal Value
Vergence Pursuit	**Focusing on object moving forward and backwards**	**0 - 100**
Spontaneous Nystagmus	Focusing on an object	Normal / Abnormal (Side)
Saccades ~ Horizontal Random	Focusing on objects randomly in horizontal axis	Normal / Abnormal (Side)
Saccades ~ Vertical Random	Focusing on objects randomly in vertical axis	Normal / Abnormal (Side)
Smooth Pursuit Horizontal ~ 0.1 Hz	Tracking objects in horizontal axis, at 0.1 Hz	Normal / Abnormal (Side)
Smooth Pursuit Horizontal ~0.75 Hz	Tracking objects in horizontal axis, at 0.75 Hz	Normal / Abnormal (Side)
Smooth Pursuit Vertical ~0.1 Hz	Tracking objects in vertical axis, at 0.1 Hz	Normal / Abnormal (Side)

Smooth Pursuit Vertical ~0.75Hz	Tracking objects in vertical axis, at 0.75 Hz	Normal / Abnormal (Side)
Predictive Saccades	Tracking an object moving in predictable manner	Percent (%) Error
Antisaccade	Moving eyes away from visual onset	% Error
OKN (optokinetic nystagmus) Trapezoidal	Tracking moving field	Normal / Abnormal (Side)
Visual Reaction Time	Reaction time to object	Seconds
Saccades and Reaction Time	Reaction time to off-center object	Seconds
Auditory Reaction Time	Reaction time to sound	Seconds
Self-Paced Saccade	Saccadic motion between two fixed targets	0 - 100
Pupil Reflex	Normal light reflex	0 - 100
Subjective Visual Vertical	Ability to perceive subjective tilt	0 - 100

12) **Data Storage**

The only data to be stored will be the results of the vergence tests and vestibular testing done during the two sessions. These results will be tied together by a subject number that will also link to the sex of the patient and age of the patient. No PHI that identifies any participant will be kept. All the previously described data will be stored on the PI's computer and used for analyses purposes in room 580 of the clinical research building at the University of Miami Medical Center located at 1120 NW 14th street, 5th Floor, Miami FL, 33136. It will be password protected, and unique identifiers used for subject protection. Data will not be distributed, except in the form of peer-reviewed publication or oral presentation maintain the confidentiality of the subjects.

13) **Data Management***

Group mean data and single subject design will be utilized. In the group mean data scoring on each of the sessions will be aggregated for each of the specific aims. First session scores will be compared to second session scores using standard statistical methods with significance defined as $p<0.05$. For the single subject design the number of subjects for each vestibular tests for each aim who have a significant difference in scores between the first and second session will be calculated and analyzed with descriptive statistics. In this way the investigators can calculate the difference between each test on the two sessions for each protocol, as it is very possible that some tests may be significantly different between the sessions and some tests will not.

Data will be stored on the PI's computer and used for analyses purposes in room 580 of the clinical research building at the University of Miami Medical Center located at 1120 NW 14th street, 5th Floor, Miami FL, 33136. It will be password protected, and unique identifiers used for subject protection. Data will not be distributed, except in the form of peer-reviewed publication or oral presentation maintain the confidentiality of the subjects. . No PHI that can identify any subjects will be kept beyond the second session of testing.

14) **Withdrawal of Subjects**
Subjects can withdraw at any time but if they withdraw their data will not be used and they will be replaced in the study by a new subject.

15) **Risks to Subjects**
The risks to the subjects will be minimal. At most, a breach of confidentiality composes the majority of the risk. We will take extensive measures to protect confidentiality and to ensure data security.

16) **Potential Benefits to Subjects**
Participating in this protocol has no potential benefit to the patients.

17) **Vulnerable Populations**
This research does not involve any venerable populations.

18) **Sharing of Results with Subjects**
Subjects can see the results of their testing after each session and can see the overall study outcome when it is prepared for scholarly presentation and publication.

19) **Setting**
All testing will take place in the University of Miami Ear and Hearing Center in the Clinical Research Building fifth floor and at a designated site on the University of Miami main campus.

20) **Resources Available**
A pair of testing goggles pre-programed to perform the test battery will be available to the investigator.

21) **Prior Approvals**
None however these same testing goggles have been used in at least two previously approved protocols at the University of Miami.

22) **Confidentiality**
We will take exhaustive measures to protect confidentiality at all times. Patients will be assigned unique identifier codes and the code will be stored separately from the subject's records. The records will be stored in a locked file in the office of PI-Dr. Hoffer. All computers used in the research will have strong password protection and the data will be accessible only to authorized research personnel. Data will be stored pursuant to time frames listed under "How Long Do I Keep Research Records" in the Investigator's Manual.

23) **Provisions to Protect the Privacy Interests of Subjects**
Subjects will be identified by an alphanumeric code designed to prevent disclosure of their identity. Information may be stored in an electronic database which will be secured with a password known only to the PI involved in this study. The database will be kept electronically until the conclusion of the study, at which time it will be printed and placed in a secure file with all other materials relevant to the study. We

will not being accessed any Protected Health Information prior to contact the subject in the clinic and neither will be accessed during the course of the proposed research, no medical record required , we will collect only name, and DOB

24) **Compensation for Research-Related Injury**
None anticipated since this is not more than minimal risk.

25) **Economic Burden to Subjects**
None anticipated.

26) **Consent Process**
Consent will be obtained by the PI, Sub-I, or study coordinator in the Ear Clinic at the University of Miami Medical Center any participants who wish to enroll in the study will be consented at the ENT clinic prior to initiating any study procedures. Informed consent will be obtained in writing via the attached documents. Participants will be taken into a private room to read the consent form and have any questions regarding the study answered by a research team member.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

No Waiver being sought

Subjects who are not yet adults (infants, children, teenagers)

Not part of subject population

Cognitively Impaired Adults

Not part of subject population

Adults Unable to Consent

Not included in subject population

References

Conn PM. "Vision." *Conn's Translational Neuroscience.* San Diego: Academic Press, 2017. 399-438.
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