Title: Dose of Vestibular Rehabilitation Required for Clinical Improvements in Individuals With Vestibular Hypofunction

NCT04851184

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Protocol and Statistical Analysis Plan.

Description:

When a potential subject is identified, the subject will be screened for appropriateness of inclusion for this study. The screen will include: questions regarding history of concussion, questions related to type of vestibular symptoms (dizziness, room spinning, imbalance, etc.), an oculomotor screen for gaze and spontaneous nystagmus, a Head Impulse Test, and a Dynamic Visual Acuity Test. Subjects will be excluded if they have a gaze nystagmus in room light, a convergence disorder detected with oculomotor screening, or are currently enrolled in vision therapy, as an adjunct treatment. These findings would indicate that the patient's diagnosis falls in a category not included in this study, or that visual disturbances would be a confounding factor during this study. If, following screening, the potential subject is determined to be appropriate for this study, informed consent will be obtained after the potential subject has all their questions answered to their satisfaction.

After informed consent has been obtained from a recruited subject, those with Unilateral Vestibular Hypofunction (UVH) will be asked to perform a 4-week intervention, while those with Bilateral Vestibular Hypofunction (BVH) or those post-concussion will each be asked to perform a 12-week intervention. Those with UVH will undergo a shorter intervention due to strong evidence that neural adaptation occurs much more quickly (usually 4 weeks) than those with BVH and history of concussion.[9,10,17-19] The intervention will consist of physical therapy visits combined with a home program of specific vestibular exercises. Each subject will be asked to attend physical therapy visits at least one time per week throughout the 4- or 12-week period.

Assessments will be performed on all groups and consist of a combination of vestibulo-ocular assessment, balance and clinical functional outcome measures, a survey regarding the usability of the virutal reality device, and surveys of subject satisfaction (see table below). Balance and functional outcome measures will include the Dizziness Handicap Inventory (DHI), Visual Analog Score (VAS) of symptoms, Visual Vertigo Analogue Scale, Functional Gait Assessment (FGA), Activities-Specific Balance Confidence (ABC) Scale, and the modified Clinical Test of Sensory Organization and Balance (CTSIB). Vestibulo-ocular assessment will be conducted using Frenzel goggles and will include tests of: Spontaneous Nystagmus, Gaze-evoked Nystagmus, Smooth Pursuit, Doll's Eyes, Head Impulse, Dynamic Visual Acuity, and Dix-Hallpike. Subjects will also perform the X1 vestibulo-ocular reflex exercise using the virtual reality device for a maximum of 30 seconds in incrementing levels. The X1 involves focusing on a stationary letter while

moving the head back and forth or up and down at approximately 1 cycle per second. If at any point the patient experiences an increase of 3 points on a scale of 0 (no dizziness) to 10 (worst imaginable) of symptoms, exercise in the device will stop. For instance, if a subject begins with a rating of 1/10 dizziness, they are instructed to stop if their symptoms reach a 4/10 or greater. Additionally, at weeks 4, 8 and 12, surveys would ask about patient comfort and level of satisfaction with regards to the intervention protocol. At the conclusion of their participation, subjects will be asked to complete the System Usability Scale to determine the usability of the virtual reality device. On each day of testing, subjects are free to skip any tests or questions they do not want to perform.

Subjects are randomly assigned to the usual rehabilitation or intervention group based on each of the following diagnostic categories: Unilateral Vestibular Hypofunction, Bilateral Vestibular Hypofunction, and post-Concussion. Therefore, there will be a total of three (3) usual rehabilitation and three (3) intervention groups (see table below). Additionally, there will be a seventh group consisting of healthy control subjects that have no history of vestibular symptoms.

Each of the three usual rehabilitation groups will perform usual physical therapy including a home VOR retraining exercise program without the use of the virtual reality headset. The VOR exercise (commonly referred to as the "X1" exercise) will involve holding a piece of paper at arm's length at eye level with an "X" written on the paper. The patient will then rotate their head right and left, reaching 30-45 degrees of excursion in each direction, while attempting to keep their eyes focused on the letter "X". They will then repeat this procedure in the up and down direction. The complexity of the background and duration of exercise will be increased via instruction from the therapist. They will be asked to keep a log of their exercises to assess patient reported compliance. In general, Subjects will be instructed to begin performing the exercises for a duration of 30 seconds at the fastest rate possible so that the 'X' remains in focus and their symptoms are tolerable. As the days progress, Subjects should increase the duration and speed of the exercises as they are able, until they can perform each set for 2 minutes at approximately 1 Hz (1 head shake per second) without any aggravation of symptoms. Once the patient has reached this point, the complexity of exercise background will be increased. Once the background complexity is increased, the patient will be instructed to again start at 30 second exercise bout durations and gradually increase until they are able to achieve 120 seconds without increase in symptoms. Once the patient achieves 120 seconds without symptoms, they will repeat the combination of exercise duration and background complexity increase in the standing position. To perform in a standing position, the patient will be instructed to stand in the corner of a room with a stable chair in front of them to provide a safe environment in which to perform the exercise and by preventing limit chance of falling.

Subjects in the three intervention groups will be asked to perform the same type of exercises as the usual rehabilitation group, but using a virtual reality device that will be issued to the patient for home use. Subjects will use a custom designed program to perform the exercises using a commercially available virtual reality device (no specialized hardware or additions to the commercially available device will be performed). Subjects will be instructed on the first day in how to operate the Virtual Reality Vestibular Rehabilitation (VRVR) program and how to properly perform the exercises. The VRVR device and software will simulate a virtual reality 'room' with an 'X' fixed in front of a wall. Six different background complexities will be offered: 1) plain grey wall, 2) checker board wall, 3) tight houndstooth wall, 4) visual flow from top to bottom, 5) visual flow to the direction of hypofunction, and 6) visual flow moving away from the nose bilaterally. Exercise sessions will start seated upright in a chair and will progress to standing per the home exercise protocol. The system will prompt the patient to begin the exercise and will automatically log the frequency and duration of exercise performed. The system will ask the patient to rate the severity of their symptoms on a 0-10 scale before and after each bout of exercise. Subjects' instruction regarding initial dose and progression will be identical to those given in the usual rehabilitation group. In addition to the general satisfaction survey given to the usual rehabilitation group, Subjects in the intervention group will also be asked to complete a survey regarding comfort, usability, and satisfaction with the VR instrument and with the VRVR software. Subjects will be asked to bring their device with them to their 4 week, 8 week, and 12 weeks appointment to transfer their de-identified data and to insure integrity of the data and device. Subjects will be asked to return the device at the end of the intervention period.

Per patient and therapist discretion, additional physical therapy visits may be scheduled to aid in patient understanding of exercise progression protocol, assess correct performance of exercise (with or without virtual reality device). Non-study related physical therapy visits may be scheduled between sessions in order to address impairments unrelated to vestibulo-ocular deficits. These may include interventions to address musculoskeletal deficits or other balance related impairments. Any additional sessions of physical therapy will be reported in order to determine possible confounding information.

There will be an additional group of healthy control subjects that will be tested for only one day. Healthy subjects will be recruited through flyers, approved email lists, and word of

mouth in the general public. This healthy control group will perform the same tests as the other groups perform on Day 1. This group will be used to compare outcomes of usual rehabilitation and intervention groups, to the function of those without disorders of vestibular function.

Statistical Analysis Plan:

Similarities in subject group characteristics will be determined using a one-way ANOVA. Characteristics will include: Age, height, weight, questionnaire scores, and functional outcome scores. A two-way Repeated-Measures ANOVA will be used for analysis of functional outcomes measures for each assessment time (0,4,8, and 12 weeks) for each group of Unilateral Vestibular Hypofunction, Bilateral Hypofunction Dysfunction, and Post Concussion Syndrome compared to their respective controls. A one-way ANOVA will be used to compare functional outcome measures of all groups on the final day of treatment only to healthy control performance. A multiple regression analysis will be used to determine the relationship between the exercise parameters and changes in outcome measures.

<table>
<tr><th>Group</th><th>Subgroup</th><th>Home Program Intervention</th><th>Visits</th><th>Test performed by all groups</th></tr>
<tr><td rowspan="3">Unilateral Vestibular Hypofunction</td><td>Usual rehabilitation</td><td>Usual Physical Therapy with patient self-reported compliance log</td><td>1) Initial Evaluation
2) 4-Weeks post</td><td rowspan="3"><u>Questionnaires</u>
Dizziness Handicap Inventory
Activities-Specific Balance Confidence Scale
Visual Vertigo Analog Scale
Visual Analog Score of symptoms
<u>Functional Assessment</u></td></tr>
<tr><td>Intervention</td><td>Home exercises using Virtual Reality Vestibular Rehabilitation</td><td>1) Initial Evaluation
2) 4-Weeks post</td></tr>
<tr><td></td><td>Usual rehabilitation</td><td>Usual Physical</td><td>1) Initial Evaluation</td></tr>
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Bilateral Vestibular Hypofunction		Therapy with patient self-reported compliance log	2) 4-Weeks post 3) 8-Weeks post 4) 12-weeks post	**Functional Gait Assessment** **modified Clinical Test of Sensory Organization and Balance** **Cervical Joint Position Error Test** Vestibulo-ocular assessment **using Frenzel goggles:** **Spontaneous Nystagmus** **Gaze-evoked Nystagmus** **Smooth Pursuit** **Doll's Eyes** **Head Impulse Test** **Dynamic Visual Acuity** **Dix-Hallpike.** VRVR Assessment **30 seconds of exercise, incrementing background complexity until an increase of 3/10 symptoms occurs** Device
	Intervention	Home exercises using Virtual Reality Vestibular Rehabilitation	1) Initial Evaluation 2) 4-Weeks post 3) 8-Weeks post 4) 12-weeks post	
Post-Concussion Syndrome	Usual rehabilitation	Usual Physical Therapy with patient self-reported compliance log	1) Initial Evaluation 2) 4-Weeks post 3) 8-Weeks post 4) 12-weeks post	
	Intervention	Home exercises using Virtual Reality Vestibular Rehabilitation	1) Initial Evaluation 2) 4-Weeks post 3) 8-Weeks post 4) 12-weeks post	

Healthy Control	Control	None	1) Single Visit	Usability **System Usability Scale**