A Double-Blind, Placebo-Controlled, Randomized Trial of Pentoxifylline for Imbalance Secondary to Insufficient Microvascular Perfusion

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Overall and Specific Objectives:

The etiologic role of insufficient microvascular perfusion in patients with balance disorders remains unclear. The treatment efficacy of hemorrheologic agents for imbalance has yet to be rigorously proven. The aim of this study is to determine if pentoxifylline, which increases perfusion at the microvascular level, improves quality of life, symptom severity, and functionality among patients with imbalance, dizziness, and vertigo secondary to microvascular insufficiency. Analysis of this data will permit determination of the appropriateness of pentoxifylline use among specific diagnostic groups and create the expertise and infrastructure for future trials among other medications and modalities for imbalance.

Background and Rationale:

The prevalence of vestibular dysfunction among American adults 40 years of age and older is 35.4%, affecting an estimated 69 million individuals.[1] Imbalance is even more common among those age 65 years and older with annual incidence of dizziness of 19.6% and vertigo present in nearly one-third of affected individuals.[2] The magnitude of balance dysfunction is anticipated to expand as the number of seniors is projected to nearly double from 2005 to 2030 to exceed 70 million individuals.[3]

Symptoms of imbalance have a severe impact on affected individuals with detrimental effects on work, travel, social and family life.[4] Large numbers of affected individuals report

reduced work efficiency and increased absenteeism, while up to 27% change jobs and 21% quit jobs due to their handicap.[4,5] Greater than one in four seniors, with balance disorders, suffer functional impact on exercise, shopping, driving, or social activities.[2] Activities of daily living are compromised in 25.7% of affected elderly individuals.[2] Limitations negatively impact autonomy, family role, work and education with an associated odds ratio for disability of 1.66.[6] Not surprisingly, depression is correlated with dizziness and there is a significant psychological impact from fear of recurrent episodes.[7,8] Dizziness and vertigo precipitate a destabilizing effect with reduced mobility resulting in deconditioning, frailty and disablement.[8]

Falls are a significant complication of imbalance, occurring in approximately 30% of community dwelling older adults every year, with 5-10% of incidents resulting in major injuries.[9] Higher rates of falls, affecting over two-thirds of individuals, are reported among older adults with symptoms of disequilibrium.[10] A meta-analysis of risk factors for falling among older adults revealed that the strongest associations with falls were history of falls, gait problems, walking aid use, vertigo, Parkinson disease, and antiepileptic drug use.[9] Older adults with disequilibrium were shown to be four times more likely to fall when compared to control subjects, and a 12-fold increase in odds of falling exists among individuals with objective vestibular dysfunction and clinical symptoms of imbalance.[1,10]

Not surprisingly, imbalance prompts many visits to physicians annually. In the United States, 7.44 million patients with dizziness or vertigo were examined in ambulatory care settings between 1999 and 2000.[11] According to the 2008 National Health Interview Survey, one-half of the 7 million individuals age 65 and older who reported dizziness or balance problems sought medical evaluation.[2] Among those individuals, 40.6% were seen by a single provider, 59.4% by two or more providers and 36% were evaluated by three or more providers, and over 700,000

visits were made to the emergency department.[12] The cause of the balance disorder was provided to 59.6% of patients.[12] Alarmingly, only 47.9% of patients felt that their balance disorder was helped by the healthcare provider.[12] The need for improved management strategies has resulted in efforts to characterize pathologies resulting in imbalance.

Postural stability involves the accurate central integration and response to input from the vestibular, visual, and somatosensory systems. Deficits can occur within any single pathway or multiple pathways simultaneously, resulting in clinical symptoms of imbalance, dizziness and/or vertigo. Many authors have reported on the frequency of vestibular pathology with wide-ranging results depending upon the method for identification of cases, diagnostic criteria utilized, how information was gathered, and other factors. Establishment of uniform diagnostic criteria for disorders are lacking and currently under consideration by the Classification Committee of the Bárány Society.[13] Two large studies reveal that up to 31.5% of individuals presenting to otolaryngologists with imbalance have symptoms secondary to idiopathic (including presbystasis), recurrent vestibulopathy, central vascular disorder, unknown peripheral vestibular disorder, and multisensory disequilibrium for whom inadequate evidence-based treatments are available.[14,15] One of the most promising novel mechanisms of imbalance in this group is microvascular insufficiency.

Arterial flow to the inner ear is delivered by small caliber vessels in the absence of collateral blood supply.[16] The target cells, including strial marginal cells, auditory hair cells, and vestibular hair cells, are rich in mitochondria and particularly sensitive to even small perturbations in flow.[17] Transient reductions in flow are hypothesized to result in acute vestibular symptoms. Chronic hypoperfusion might result in subclinical deficits that eventually become symptomatic in isolation or synergistically with other deficits. Significant losses in spiral

ligament volume and stria vascularis volume have been demonstrated in individuals over the age of 60 as compared to those under the age of 40 years.[17,18] Eighty to ninety percent of individuals 70 years of age and above have evidence of semicircular canal dysfunction, 50% had abnormal saccular function and 20% had abnormal utricular function.[17,18] Interestingly, histologic studies show a greater loss of vestibular hair cells in the cristae ampullares of the semicircular canals relative to the otolithic maculae, suggesting that hair cell loss might be the mechanism of reduced function.[7,18] Human temporal bone studies and animal models support subtle and highly prevalent pathologies in the elderly, such as ischemia, as the cause of such losses with aging.[17,19,20] While reduction in microvascular flow to the inner ear might account for vestibular losses in some presentations, inadequate perfusion centrally can produce identical symptoms and diffuse microvascular insufficiency can lead to multisensory deficits.

Reduced blood flow to the cerebellum and lateral medulla can present as isolated vertigo, mimicking labyrinthine dysfunction and coexist with other symptomatic microvascular insufficiency.[16] Seventeen percent of individuals with cerebral microangiopathy, in the absence of peripheral lesions, have vertigo and 31% of individuals with cerebrovascular disease experience at least one episode of isolated vertigo.[21,22] Synergistic defects in multiple systems (visual, neurologic, vestibular, and central nervous system) are particularly common in older individuals and can result from microvascular dysfunction, particularly among diabetics who suffer accelerated microangiopathic effects.[1,23] Therefore, reduced microvascular perfusion is a possible uniting mechanism among multiple causes of imbalance including presbystasis, multisensory losses/disequilibrium, bilateral vestibulopathy, central vascular vertigo, and peripheral vestibular hypofunction of unclear etiology.[16,19,23,24]

Preliminary work/results:

Treatment efficacy with medications that improve microvascular blood flow to the inner ear is the most convincing evidence for the role of vascular insufficiency causing imbalance. Betahistine has demonstrated efficacy for treatment of Ménière's disease and other vertiginous syndromes in randomized, placebo-controlled trials.[25,26] Piracetam can alleviate vertigo after head injury, vertigo in vertebrobasilar insufficiency and in peripheral vestibular disorders.[27] Ginkgo biloba extract EGb 761 is effective for treatment of vestibular and non-vestibular vertigo in randomized placebo controlled trials.[28] When betahistine and ginkgo biloba extract EGb 761 were directly compared in patients with peripheral vertigo not otherwise specified or vertiginous syndrome not otherwise specified similar efficacy was observed in both groups with fewer adverse effects from ginkgo biloba 761.[28]

Studies have also investigated the use of pentoxifylline for vascular causes of imbalance as it is known to increase erythrocyte flexibility and decrease blood viscosity, thereby improving microvascular blood flow.[29] Cesarone et al. performed a placebo–controlled, randomized trial, of pentoxifylline for vascular inner ear disease using a dose of 1800 mg per day and found a statistically significant increase in cochlear blood flow of 287.5% in the pentoxifylline group versus 168% in the placebo group.[30] Importantly, the increase in flow brought the cochlear flow in the treatment group up into the reported normal range while the placebo treated individuals flow remained reduced.[30] In a separate report utilizing the same patient population, Incandela et al. found a 44.1% larger reduction in symptoms including vertigo, dizziness, tinnitus, and hearing loss in the pentoxifylline group than the placebo group.[31] In another study, Hartmann et al. studied regional cerebral blood flow, as measured by xenon 133 inhalation, among patients with reduced cerebral blood flow due to vascular disease in an open, randomized controlled, format.[32] The authors found that use of pentoxifylline and the ergot alkaloid co-dergocrine

mesylate resulted in increased flow but a much more pronounced effect was seen with pentoxifylline.[32] Interestingly, the pentoxifylline treated group showed preferential improvement in flow among the more ischemic brain tissue, and patients reported improvements in sleep disturbances, vertigo, and tinnitus.[32] The selective improvement in flow among areas that are relatively ischemic is felt to be associated with the hemorrheologic mechanism of pentoxifylline and is proposed to be unique to drugs that work in this way without such beneficial effects in other medications such as vasodilators.[32] While these reports suggest that pentoxifylline use is beneficial, small numbers of patients were included and non-validated instruments were used to measure symptomatic improvement. Therefore, further investigation into the efficacy of pentoxifylline for treatment of imbalance due to vascular etiologies is necessary, including identification of particular subsets of patients most likely to benefit from treatment. Many trials in varied populations demonstrate that pentoxifylline has an excellent safety profile with minimal increase in adverse effects over placebo making it an ideal agent to study and use if efficacy is demonstrated.[29,30,32]

Project design and Procedures:

Adults, 18 years of age and over, presenting to the University of Missouri Department of Otolaryngology Head and Neck Surgery with chief concern of vertigo, dizziness, or imbalance will be considered for study. All individuals will undergo comprehensive clinical evaluation including otoscopic examination and testing of cerebellar function, gait observation, and dix hallpike maneuver. Additionally, all individuals will receive an audiogram and complete pre-intervention balance questionnaires, per standard of care. MRI of the brain/internal auditory canal as well as formal vestibular function testing will be conducted at the discretion of the enrolling provider. Individuals diagnosed with multisensory losses, presbystasis, bilateral

vestibulopathy, central vascular insufficiency, small vessel circulatory disease, generalized imbalance, and idiopathic peripheral vertigo scoring at least 16 on the Dizziness Handicap Inventory will be offered participation in the study. Patients must have sufficient English skills to complete the required surveys.

Potential participants will be excluded if any of the following diagnoses are made: benign paroxysmal positional vertigo, Ménière's disease, vestibular migraine with headache, intracranial mass, perilymphatic fistula, or multiple sclerosis. In addition, individuals will be ineligible if there is history of cholesteatoma, prior ear surgery other than myringotomy and tube placement, prior radiation therapy to the head and neck, or previous use of vestibulotoxic medications where the enrolling provider determines the drug exposure to be the cause of imbalance. Use of blood thinning medications or intolerance/allergy to pentoyifylline or methylxanthines, as well as recent cerebral or retinal hemorrhage (past 3 months), will result in exclusion. Females must not be pregnant or lactating and individuals must use adequate contraception during the study period. Females of child bearing potential will be administered a pregnancy test prior to starting the study medication.. Use of any other medications to control vertiginous symptoms and participation in vestibular rehabilitation during the study period will be prohibited.

Patients electing to participate will be randomized to receive either 400 mg of pentoxifylline three times daily for 12 weeks or placebo three times daily for 12 weeks. Allocation will be made randomly and providers and patients blinded to treatment arm. Study medications will be provided to participants at no cost, and plant cellulose will be used as placebo. Outcomes will be measured in three domains: quality of life (handicap), symptom severity, and functionality. Data will be obtained prior to initiation of therapy and at designated time intervals into treatment: 4-6 weeks and 12-14 weeks (Figure 1).

The Dizziness Handicap Inventory will be used to assess quality of life, the European Evaluation of Vertigo for symptom severity, and the Vestibular Activities and Participation Measure to assess functionality. Patients will be asked to report the number of falls in the preceding 3 months as well as document any falls during the study period. Finally, participants will be queried regarding their working status and the number of missed days due to vertiginous symptoms in the past three months prior to participation and during the study period. Head or neck imaging and vestibular function study results will be assessed by chart review at the conclusion of the study. The following adverse effects will be recorded at each clinic visit: angina/chest pain, arrhythmia/palpitation; flushing; abdominal discomfort; belching/flatus/bloating; diarrhea; dyspepsia; nausea; vomiting; agitation/nervousness; dizziness; drowsiness; headache; insomnia; tremor; blurred vision. Medical comorbidities will be reviewed to facilitate subgroup analysis. Determination of treatment effect will be made through implementation of ANOVA testing, through IBM SPSS Statistics software.

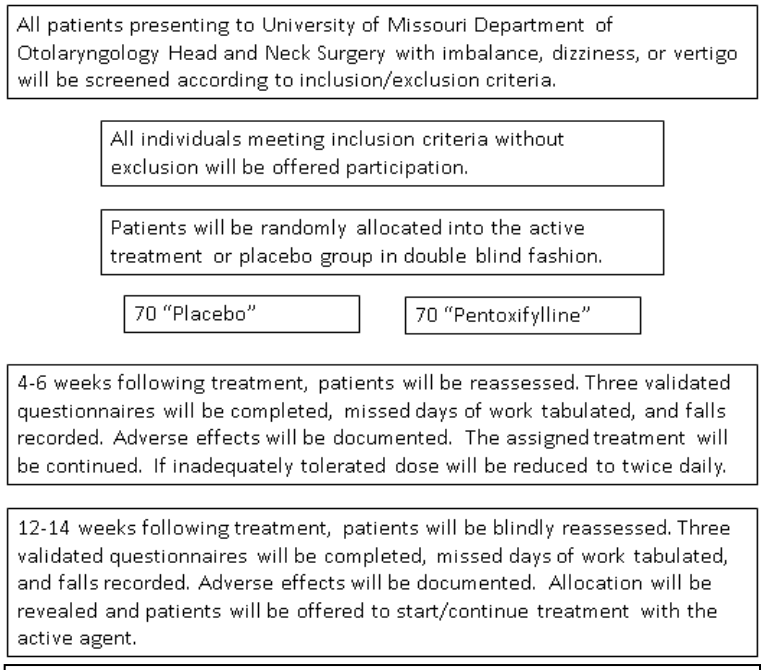

Figure 1: Study Design

Based upon reported data for improvement with pentoxifylline and placebo effect, at an alpha level of 0.05 and beta of 0.2, a power of 80% can be reached with 70 patients per treatment group (140 patients total) .[33] We will enroll an extra 20 patients to patient dropout for a total of

160 patients to be enrolled. According to present clinic patterns, we anticipate target enrollment will be reached in approximately 18 months.

Data Handling

All data will be collected both in hard copy and electronic formats. Hard copy data will be stored in a locked office in a locked filing cabinet. Electronic data will be stored on a secure MU network drive that is encrypted and password protected. The research coordinator is responsible for access to both of these locations. Additionally, consents are signed electronically and stored on the secure network drive.

Significance of Research to the Specific Field and Stature of the University:

Vestibular dysfunction affects over one in three Americans 40 years of age and over and is more common among older individuals. Projections over the next 15years forecast significant increases in the magnitude of imbalance, vertigo and dizziness, yet extensive diagnostic possibilities and incomplete understanding of the causes of imbalance result in 52.1% of individuals reporting that their balance problem was not helped by their healthcare provider. With evidence supporting microvascular insufficiency as a contributing or causative factor in up to one in three individuals, it warrants rigorous evaluation as a method to improve the profound negative impact of imbalance on independence, quality of life, healthcare utilization and societal contributions. Determination of efficacy will permit improved understanding of the role of microvascular insufficiency in vestibular dysfunction, and a positive finding would represent a landmark trial in medicine with the possibility to redefine the therapeutic paradigm of selected balance disorders. Effectiveness would almost certainly spark future comparative studies of other medications and modalities to treat imbalance secondary to insufficient microvascular perfusion and the University of Missouri Hearing and Balance Center would be a highly competitive site

for future external funding through grants, collaboration with pharmaceutical companies and other government agencies as a direct result of the expertise and infrastructure developed through this effort.

Resources and environment:

The Hearing and Balance Center at University Hospital and Clinics provides a steady flow of new patients meeting eligibility criteria. Potential participants will be identified by providers in the University of Missouri Department of Otolaryngology Head and Neck Surgery. The research division of the University Hospital and Clinics Pharmacy will order, prepare, and dispense study drugs according to a blinding scheme. A senior research coordinator in the Department of Otolaryngology Head and Neck Surgery will assist with patient enrollment, facilitate data collection and perform statistical testing once results are available. A resident physician within the University of Missouri Department of Otolaryngology Head and Neck Surgery will help oversee the project and facilitate completion during a 1 month dedicated research block in the 2015-2016 academic year.