Clinical Research in Neurostimulation and Movement Disorders

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Evaluation of Spinal Cord Stimulators in Patients with Paralysis Post Spinal Cord Injury

Spinal cord injuries offer significant challenges for both patients and physicians. Patients affected by this form of injury are often left with debilitating and potentially permanent disabilities or deficiencies, which cause hardships in normal daily life. For the physician, the challenge is in the limited scope of interventions that we have available to help our patients deal with these issues. New interventions are being developed that show promising results in this field. My large multidisciplinary team includes: neuroradiologists, neuroscientist, physical medicine and rehabilitation, international research fellows, and UT students. We are assessing the effectiveness of a Spinal Cord Stimulator device in increasing the functional capacity of a spinal cord injury patient with lower-extremity paralysis, namely regaining the ability to stand or step. We are currently in the final step by submitting the Investigational Device Exemption application for FDA approval so we can start working on this project.

Effects of Spinal Cord Stimulation on Sensory Perceptions of Chronic Pain Patients

This is an international, multicentric project with CHU de Québec – Hôpital de l’Enfant-Jésus. Canada. According to the International Association for the Study of Pain (IASP), pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described regarding such damage.” Chronic pain is defined as any pain lasting more than three to six months and is resistant to conventional treatments. A literature review published in 2012 reveals that the prevalence of chronic pain in the general Canadian population is ranging from 29% to 44.4%. We are evaluating the effect of spinal cord stimulation on the sensory perception of chronic pain patients.

Utility of Diffusion Tensor Imaging in Pre-Operative Evaluation of Patients with Normal Pressure Hydrocephalus and Chiari Malformation

Currently, our pre-operative evaluation strategies for evaluating patients with NPH and Chiari malformations are limited to clinical symptomatology and basic imaging results. However, these patients often require surgical treatment for symptomatic relief, and appropriate decision making prior to surgical intervention leads to vastly superior outcomes.

For patients with NPH, the clinical symptomatology (the traditional “Wet, Waky, and Wobbly,” or rather
urinary incontinence, dementia, and gait disturbances) is not always present. Also, imaging findings (including both Computed Tomography [CT] and MRI) are generally non-specific. Thus, we are generally forced to perform a lumbar drain trial—an uncomfortable and cumbersome procedure requiring a lumbar puncture—to characterize the opening cerebrospinal fluid (CSF) pressure in order to confirm the diagnosis prior to surgical intervention. At this stage, no imaging study has been definitively proven to be able to diagnose NPH pre-operatively with accuracy.

A similar conundrum exists for patients with Chiari malformations. These patients—much like NPH patients—require surgical treatment. However, poor patient selection for operative management can be dangerous or unfruitful. Due to the often non-specific constellation of symptoms that affects these patients, an accurate pre-operative diagnosis of Chiari is essential. Unfortunately, we are relying on limited imaging modalities when evaluating these patients, which creates the possibility for incorrect decision making pre-operatively.

Therefore, due to the difficulties presented above, better diagnostic methods and more accurate predictors of surgical success are needed for the treatment of these two patient populations.

We are assessing the utility of Diffusion Tensor Imaging (DTI), a type of Magnetic Resonance Imaging (MRI), in the pre-operative and post-operative evaluation of complex Neurosurgical pathologies, namely Normal Pressure Hydrocephalus (NPH) and Chiari malformations.

**A Cerebrospinal Fluid and Salivary Biomarker in Moderate to Severe Traumatic Brain Injury**

Currently, there is limited understanding regarding the prognosis for patients with moderate to severe TBI, and its management is complicated. Therefore, having another tool such as CSF and saliva biomarker in our arsenal would greatly enhance our assessment and treatment of this patient population. So based on ongoing work in the Giovannucci, Chiaia, and Hensley labs indicated that the brain-specific CRMP2 protein undergoes proteolytic fragmentation after blasted wave-induced brain injury in animal models and that within hours a 55 kDa CRMP2 fragment increases in saliva. We are evaluating this Cerebrospinal Fluid and Salivary Biomarker in Moderate to Severe Traumatic Brain Injury.

**Evaluation of mDia Agonists as Possible Therapeutic Agents for Primary Malignant CNS Tumors**

Glioblastoma’s (GBM) extensive invasive capacity makes it resistant to surgery, radio- and chemotherapy, and thus makes it lethal. In vivo, GBM invasion is mediated by Rho GTPases through unidentified downstream effectors. Mammalian Diaphanous (mDia) family formins are Rho-directed effectors that regulate the F-actin cytoskeleton to support tumor cell motility. Our recent work in human immortalized GBM cultured cell lines revealed a role for mDia formins in regulating GBM cellular migration and invasion in vitro and in an ex vivo rat brain slice model. Due to their critical roles in regulating tumor cell migration and invasion, we evaluated mDia inhibition and activation to determine whether either strategy has potential as a clinical intervention in GBM treatment. Our findings demonstrated that mDia agonism, through use of small molecule activators called intramimics, or IMMs, represented an effective and clinically-relevant GBM therapeutic strategy. The proposed study will now expand upon these in vitro/ex vivo experiments by testing the requirement for mDia functional activity in clinically-relevant patient-derived glioblastoma spheroid invasion assays. We will also evaluate the potential of IMMs for treatment of patient-derived xenografts (PDX) grown in immunocompromised mice. We are assessing the effectiveness of mDia agonists as a clinical intervention in the treatment of patient-derived Glioblastoma Multiforme (GBM) tumors as well as other primary malignant tumors of the CNS grown in immunocompromised lab mice.

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**Clinical Research Snippets**

**Long-Term Use of Oxygen for COPD**

**By: Douglas Federman, MD**

“COPD” chronic obstructive airway disease is common and is responsible for at least 120,000 deaths every year in US. Previous studies have shown decreased morbidity and mortality in severe COPD patients with resting hypoxemia of 88 percent or lower or arterial oxygen saturation below 55 mmHg. However the benefit in patients with moderate hypoxemia at rest of 88-93 percent or exercise induced hypoxemia between 80-90 percent is unknown. Currently these patients are prescribed continuous and portable oxygen routinely. This month we bring a well randomized controlled study of use of oxygen in this latter group and assess its benefits.

This is a multicenter study recruiting patients with
moderate hypoxemia with resting oxygen saturation between 89-93 percent or exercise induced desaturation after a 6 minute walk to 80-90 percent. Patients agreed to abstain from smoking during the study. One group was randomized to either continuous supplemental oxygen or supplemental oxygen during exercise and sleep only. Oxygen was titrated to pulse oximetry of greater than 90 percent. The control group did not receive supplemental oxygen but was monitored similarly.

Over 5 years 738 patients were randomized amongst 42 centers. Resting desaturation was present in 18 percent of patients, exercise-induced desaturation in 43 percent, and both types of desaturation in 39 percent. Median follow up was 18.4 months. A time-to-event analysis revealed no difference between the groups and subgroups in mortality or hospital admissions.

This was a well-designed study and explored quality of life, anxiety, depression, and functional status as well. This study clearly refutes the benefit of oxygen supplementation in patients with moderate resting hypoxemia between 88-93% and in patients with exercise induced hypoxemia between 80-90 percent. This result may be affected by improved treatment modalities of underlying diseases in these patients.

New Clinical Trials

Imperial trial - A randomized trial comparing the ELUVIA drug-eluting stent versus Zilver PTX stent for treatment of superficial femoral and / or proximal popliteal arteries.
Dr. Burket - Medicine

A Double-Blind, Controlled Phase 2B Study of the Safety and Efficacy of Modified Stem Cells (SB623) in Patients with Chronic Motor Deficit from Ischemic Stroke.
Dr. Jumaa - Neurology

IRB Corner

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