Neuromuscular Mechanisms Underlying Poor Recovery From Whiplash Injuries

NCT02157038

ID: STU00090769

Study Protocol & Analysis Plan

11/30/2017

Study Protocol:

Consented subjects will be invited to attend four sessions (within one week and then again at 2weeks, 3-months, and 12-months post-injury) at Northwestern University's research-imaging center to complete the questionnaires and undergo MRI of the spinal cord and select muscles of the spine and lower extremities. The selection of four time points will permit the determination of time-dependent degeneration of neck and leg muscles with 3D fat/water imaging and any cellular level changes in the white matter pathways of the cervical spinal cord with MTR as well as any temporal changes in psychosocial factors (e.g. coping, expectations, anxiety and depression). The maximum plantar flexion torques and twitch interpolation measures in the lower extremity, which are more technical and time-consuming than the imaging measures, will be completed at the 2-week, 3-month, and 12-month follow-up sessions.

Subjects will then be classified into one of two groups, based on percentage scores from the Neck Disability Index (NDI), at the end of the study at 12-months post-injury. The two groups will be categorized accordingly: recovered/mild symptoms (2–28%) and moderate/severe symptoms (>30%). This grouping has been validated and widely used in whiplash . A full-time research assistant will be responsible for categorizing these two groups and the individual performing the MRI analyses (JE) will be blind to this categorization, thus controlling for any perceived classification bias. Upon completion of the first session (< 1 week post injury), subjects will be scheduled to return for a second MRI scan at 2-weeks post MVA. During all follow-up sessions (2-weeks, 3-months and 12-months post MVA), subjects will undergo repeat MRI scans as well as complete all questionnaires. The plantar flexion torque and twitch interpolation measures will be completed at the 2-week, 3-month, and 12-month follow-up sessions.

Socio-demographic and MVA related details Questionnaires used in our current research will be employed at each time point to record: known psychosocial factors (e.g., coping, expectations, anxiety and depression), current symptoms at each follow-up assessment; work and disability status, nature of treatment received initially and any ongoing treatments; details of drug therapy; compensation status, and lawyer involvement. Demographic information will be collected at baseline only to record: socio-demographic details; accident related information (direction of impact, presence of headrest or active head restraint system, position of head at time of impact, preparedness for injury, driver, passenger); initial and past history of neck pain/headaches as recall of these baseline demographic factors will deteriorate over time.

It is recognized that self-report collision data as well as reports obtained from witnesses to the crash is not altogether scientifically reliable. As such, more quantitative collision data could shed

light on the link between occupant kinematics, potential injurious mechanisms and the findings from the advanced imaging protocols proposed in this application. For example, data from rear impact collisions, such as photos, repair estimates, and repair invoices of both involved vehicles could be used to estimate the collision severity and this would help determine relationships between rear-impact forces, advanced MR findings and recovery rates for patients with whiplash of varying severity. With the study participant's approval, we will send a member of our research team to capture photos of the damaged vehicle. While this is not a primary focus of this study proposal, we will set focus (with expert consultancy from Dr. Gunter Siegmund, PhD) on collecting collision data for all involved vehicles to correlate with our MRI findings. Furthermore, Dr. Siegmund will assist in future granting applications aimed at collecting and analyzing available quantitative collision parameters from vehicular event data recording (EDR) devices, as it remains plausible that such quantitative data is directly related to injury of vital structures throughout the cervical region, including the cervical spinal cord.

Measure of pain-related disability (obtained at each time point) The Neck Disability Index (NDI) - a 10-item validated questionnaire 45 that has been widely used in studies of whiplash will be collected at each time point and scored as a percentage (x/100). Higher scores equal more pain-related disability.

Measures of Psychological distress (obtained at each time point)
1) Tampa scale of Kinesiophobia (TSK) - is a 17-item self-report measure of fear of re-injury due to movement (kinesiophobia), and has been shown to be a robust tool for traumatic neck pain.
2) The Vanderbilt Pain Management Inventory (PMI) - is an 18-item self-report measure that assesses how often chronic pain patients use active (7 items) or passive (11 items) coping strategies when their pain reaches a moderate or greater level of intensity.
3) The Centre for Epidemiological Studies Depression Scale (CES-D 10) - has been designed for use with non-psychiatric patients and is used extensively with disabled populations and persons with pain as a screen for depressive illness.
4) The Impact of Events Scale (IES) - is a 15-item questionnaire measuring a stress response related to a particular event. The IES has been validated in studies investigating emotional responses to acute trauma, including SCI , and shown to have predictive capacity of poor functional outcomes following whiplash .
5) Dysphagia Handicap Index (DHI), Eating Assessment Tool (EAT-10)

Aim 1 Fatty deposits in the neck and leg muscles will be visualized using the 3D multi-echo Dixon fat/water gradient echo approach developed by our group and detailed below.

A number of imaging techniques, based on the different precessional frequencies of fat and water protons can be used to quantify fat and water concentration. We recently expanded our previous program using T1-weighted MRI by using an accepted 3D multi-echo gradient echo acquisition

to collect the data required for the analysis of phase related to the precessional differences in fat and water. The fat/water separation algorithm uses the variable projection (VARPRO) method with four or more echoes (8 in our study at 3T) with non-uniformly spaced echo times (phase shifts between water and fat) to optimize fat/muscle measures. The reconstruction process has been automated in the Siemens sequence environment so that fat-only, water-only, and calculated in-phase and opposed-phase images are created. This technique is very similar to the method developed by Reeder et al. for imaging fat and water in various bodily organs/tissues.

First, a 3D-multi-echo, gradient echo fat-water separation MRI technique will be performed on all 60 subjects at each time point. The two short MR examinations will include: the cervical spine (from the cephalad portion of C3 to the caudal portion of C7) and the bilateral lower extremity (quadriceps, hamstrings, dorsi and plantar flexors). For the cervical spine, a standard 12-channel head coil and a dedicated neck coil of the manufacturer will be used as a receiver coil. A localizer scan and a T2-weighted sagittal turbo spin echo sequence will be performed. The FLASH based axial gradient echo sequence parameters will be: TR=23.81ms, 8 echo times with a spacing of 1.78ms starting at 1.36ms. A single slab will be placed over the cervical spine with 36 partitions and a partition thickness of 3mm with slab oversampling of 22% to prevent aliasing in the 3D direction. The in-plane resolution will be 1.4mm using a rectangular field of view (FOV) of 75% resulting in an acquisition time of 2:06 minutes.

Regions of interest (ROI) will be manually drawn using Analyze Software (v. 11.0) of the bilateral neck extensor muscles (multifidus, semispinalis cervicis, semispinalis capitis and splenius capitis) at the most cephalad portion of each respective vertebral level (C3-C7). The upper trapezius will not be included in this analysis, as this would require a larger field of view at the lower cervical segments where the muscle attaches to the shoulders. The muscles at each level as well as the right and left sides will be combined for the analysis, as our previous research has not identified significant laterality differences in neck muscle fat concentrations in whiplash. A similar FLASH based gradient echo sequence (FOV adjusted to fully cover the anatomy) will be used for the lower extremity muscles using a 16 channel body array surface coil. Both the left and right lower extremities will be acquired in a single acquisition. Localizer scans will be used to obtain the fat/water data in the axial plane perpendicular to the bone. A total acquisition time of 30 minutes for the neck and lower extremity muscle groups is expected. Furthermore, we accept that reduced activity levels could account for, or contribute to, muscle degeneration following whiplash. To control this, we will prospectively collect day-to-day ambulatory activity for a total of two-weeks between the 2nd and 3rd time points in all subjects using a Fitbit Zip wireless activity tracker, which is a small self-contained device that clips securely to an article of clothing.. We will also take into account fluctuations in daily outdoor activity due to seasonal weather changes in Chicago.

Aim 2 The objective is to investigate, in prospective fashion, the presence of acute neural injuries and subsequent losses of descending white matter pathways at the cervical spinal cord using Magnetization Transfer Ratio (MTR); a technique that improves upon currently used MRI applications to measure the neuronal density of the spinal cord.

Characterizing the demyelination/degeneration of ascending and descending white matter spinal pathways in patients with SCI is crucial for assessing prognosis of functional rehabilitation. Magnetization Transfer imaging provides a more sensitive and specific marker of white matter pathology in the cervical cord when compared to traditional T1- and T2-weighted signals. Furthermore, MTR measures of the ventrolateral spinal pathways in SCI have shown to be predictive of motor disability levels, suggesting a non-invasive MRI measure of cord degeneration and determination of impairment is possible. The rationale of Aim 2 is therefore to provide new knowledge elucidating the differential loss of neural substrate in the white matter pathways as it relates to both the expression of muscle degeneration and deficits in volitional muscle activation. Reductions in MTR in the ventrolateral portion of the cord may indicate a disruption of descending motor tracts resulting in a reduced ability to activate a motoneurons, which could explain persistent muscle weakness and fatigue. Results from this aim will enhance the predictive profile of whiplash with precise information characterizing processes related to and associated with reductions in volitional muscle activation and muscular fatigue.

For this aim, MTR of the cervical spinal cord white matter will be quantified using magnetization transfer MRI detailed below. Following the fat/water data collection in the neck and lower extremities, 2 additional scans will be run to determine the MTR in the white matter regions of the cervical cord. The 2D slices will be oriented parallel to the disk planes of C4-C6. In order to improve signal to noise we will employ the imaging method of Multiple-Echo Data Image Combination (MEDIC). MEDIC samples the magnetization at several echoes and combines them to improve the signal-to-noise without increasing scan time or increasing specific absorption rate (RF heating of the patient). The MT scan has the parameters of TR/TE eff /Flip angle of 300ms/17ms/40 combining three echoes, a matrix size of 384 and a FOV of 180mm with an in plane resolution of 0.5mm and a slice thickness of 4mm, collecting 11 slices. The scan uses two averages with parallel imaging (GRAPPA) with an acceleration of 2 to keep scan time down to reduce motion related artifacts. The MT pulse is applied 1.5kHz off-resonance with a large flip angle (540 in our implementation) and long duration (10ms) to saturate the bound water pool. The MT scan duration is 4 minutes. The non-MT scan is identical except that the MT saturation pulse is turned off and run as a separate acquisition. The MTR will then be calculated on a voxel by voxel basis using the formula of MTR= 100*(non-MT – MT)/non-MT. ROIs at each vertebral level will be placed in the ventral, right, left and dorsal spinal columns.

Aim 3 For this aim, plantar flexor torque responses to maximum voluntary contractions (MVC) will be measured for assessment of each subject's bilateral ankle strength. With the knee

extended, measurements of the volitional strength of the plantar flexors will be made from an ankle position of 0° (neutral). Five trials each of maximal voluntary plantar flexion will be performed upon verbal cue. All participants will be verbally instructed and motivated to maintain these maximum contractions for 3-8 seconds. Visual feedback of torque production will not be provided. Peak MVC torque responses, duration about the peak, and average sustained torque produced during the MVC will be measured and averaged over the five trials. To account for any differences in MVC duration due to instruction or reaction time variations from subject to subject, measurements involving torque over time will be normalized to instruction duration and reported in relation to time in seconds. The test foot will be secured to a footplate, which is attached to a 6-degree of freedom load cell mounted to the Biodex system described above. Plantar flexor CAR's will be determined using the burst superimposition technique and calculated as described directly above. Fatigue will be assessed using the 5 repeated maximal effort contractions as described above. Though this is an abbreviated duration as compared to previous work, we believe 20 repeated maximal efforts is too demanding for patients given the acuteness of injury in this case.

Statistical Plan

Statistical Considerations for Aim 1:
Functional recovery will be measured using the NDI percentage score at 12 months. Participants will be sub-grouped based on the following: 2-28% mild/recovered: > 30% moderate/severe symptoms 12,78 . Mixed model analyses for repeated measures with a time-invariant group effect, a categorical time effect and a group by time interaction term, will be used to compare the two recovery groups with respect to the changes over time in the dependent variables. Separate analyses will be done for each dependent variable. Age, Body Mass Index (BMI) and time specific activity levels will be used as covariates in the analyses. Sample sizes of 27 in the severe group and 63 in the recovered group (total of 100 with an expected 10% dropout resulting in 90 with complete follow-up) have 80% power to detect a difference in mean MFI of 0.66 standard deviations, assuming a two-tailed test and a Type I error rate of 0.05. Previous results for neck muscle fatty infiltration data indicated a standard deviation of 3.6% with a mean at 3 months of 17.0% fat in the mild/recovered group, and 25.1% fat in the moderate/severe group (difference =8.1%). Assuming continued progression of neck muscle fat in the moderate/severe group, the study is powered to detect differences between the moderate/severe group and the mild/recovered group at 12 months of 2.4% (0.66 x 3.6), which is smaller than the previously observed difference of 8.1%. However, power may be decreased due to the multivariate analyses performed when covariates are included in the model. The effect of adjustment is difficult to predict a priori since one or both of the estimated mean and the residual variation may be affected by adjustment. Our pilot data on plantar flexor muscle fat indicated a standard deviation of 0.5% with 7.0% fat in the mild/recovered group, and a mean (SD) of 14.5% (2.1%) in the moderate/severe group with varying duration of symptoms (difference = 7.5%). The study is

powered to detect differences between the moderate/severe group and the mild/recovered group at 12 months of 1.4% (0.66 x 2.1), which is smaller than previously observed difference of 7.5%. To determine whether changes in fat content are mediated by other factors, a small number of covariates selected from the measures of psychological distress, activity levels, age or BMI will be included in an analysis of covariance to determine whether results seen in the unadjusted analyses are maintained or attenuated.

Statistical Considerations for Aim 2

Statistical analyses for Aim 2 will be similar to those of Aim 1, where mixed model analyses for repeated measures with a time-invariant group effect, a categorical time effect, and a group by time interaction term will be used to compare the two groups with respect to the changes over time in MTR of the cervical spinal cord white matter pathways. Cross-sectional comparisons will be performed at each time point by Bonferroni-corrected t-tests. Sample sizes of 27 in the severe group and 63 in the recovered group (total of 100 with an expected 10% dropout resulting in 90 with complete follow-up) have 80% power to detect a difference in mean cord MTR of 0.66 standard deviations, assuming a two-tailed test and a Type I error rate of 0.05. Previous data 16 for cervical spinal cord MTR indicated a standard deviation of 4.7 with a severe patient mean of 26.8 and a control group mean of 32.4 (difference=5.6). This study is powered to detect an MTR difference between the moderate/severe group and the mild/recovered group of 3.1 (0.66 x 4.7), which is smaller than the previously observed difference of 5.6%, provided the mild/recovered group exhibits MTR levels similar to previously reported values from healthy controls. A similar strategy to perform adjusted analyses as described in Aim 1 will also be used in this aim.

Statistical Considerations for Aim 3

Mixed model analyses for repeated measures with a time-invariant group effect, a categorical time effect and a group by time interaction term, will be used to compare the two recovery groups with respect to the changes over time in the dependent variables of CAR and volitional torque. Separate analyses will be performed for each dependent variable. Age, BMI, and time specific activity levels will be used as covariates in the analyses. Sample sizes of 27 in the severe group and 63 in the recovered group (total of 100 with an expected 10% dropout resulting in 90 with complete follow-up) have 80% power to detect a difference in mean CAR's of 0.66 standard deviations, assuming a two-tailed test and a Type I error rate of 0.05. Previous results for CAR data are given above with a mean difference of 0.07 (0.96 – 0.89) and a standard deviation of 0.04. The study is powered to detect differences between the moderate/severe group and the mild/recovered group at 12 months of 0.03 (0.66 x 0.04), a difference smaller than the previously observed difference of 0.07. To determine the influence of psychosocial factors, age, BMI, and activity level on muscle activation and fatigue in the two groups, covariate adjustments, as

described in Aim 1, will be used to determine maintenance or attenuation of effect over time or by group.