Impaired Performance on the Angle Board Test Is Induced in a Model of Painful Whiplash Injury but Is Only Transient in a Model of Cervical Radiculopathy

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ABSTRACT: Although clinical studies report motor impairment associated with some painful injuries of the neck, assessment of motor function in animal models has been largely limited only to studies of direct trauma to the nervous system. The incline plane test was modified to evaluate motor function in two rodent pain models of facet joint distraction (FJD) and nerve root compression (NRC) injury ($n = 5$/group). Sham groups were also included as controls. Motor function was measured using the modified inclined plane test with rats facing downward before surgery (baseline) and following surgery on days corresponding to when mechanical sensitivity is established and remains elevated. Mean baseline values of the board angle inducing slip for FJD ($45.8 \pm 3.1^\circ$) was significantly greater ($p = 0.014$) than that for NRC ($43.5 \pm 2.5^\circ$), but baseline measurements did not vary for either group over time. No changes in motor function were found for shams. Motor function after FJD significantly decreased ($p < 0.001$) at days 1 and 7 after injury. In contrast, at day 1 after NRC injury, slip occurred at significantly lower ($p = 0.0016$) incline angles, but returned to baseline levels by day 7. These results show motor function impairment is induced following painful FJD and suggest the incline plane test offers utility to evaluate functional deficits in painful injuries. J Orthop Res 29:562–566, 2011

Keywords: motor function; pain; neck; incline plane; impairment

Traumatic injuries to the neck that produce chronic pain are often associated with motor deficits. Such clinical disorders can result from injuries to the spinal ligaments and/or the nerve roots and are typically characterized by pain and sensitivity to pressure in the neck and shoulders that can radiate to the head, arm, and into the hands and fingers.[1–9] For example, in whiplash patients, neck pain is associated with impaired cervical movement control, weakness of the cervical and upper limb musculature, reduced head/neck proprioceptive sense, and whole body postural control deficits.[8,10–17] Depending on the cervical level of the affected nerve root in radiculopathy, motor deficits can also be accompanied by weakness of the ipsilateral shoulder and/or arm muscles.[1,18]

Our lab has developed separate pain models in the rat that mimic the injury and pain symptoms observed in human neck pain patients with facet-mediated whiplash injuries[19–22] and cervical radiculopathy.[22–25] Specifically, distraction of the bilateral facet joints and their capsules that simulates joint loading during whiplash induces significant sustained mechanical allodynia and hyperalgesia in both the shoulders and forepaws.[19–22] In addition, a transient compression of the unilateral cervical dorsal root also produces significant behavioral hypersensitivity in the ipsilateral forepaw.[22–25] These and other injury models have been used as platforms to elucidate relationships between tissue injury, pain, and mechanisms of nociception. In fact, several models of cancer, inflammatory, and repetitive strain injury-induced pain in the rodent have also evaluated motor function via measurements of forelimb grip force and reach rate.[26–29] Yet, despite the clinical evidence suggesting associated motor impairment with these disorders, no work has evaluated motor function in models of pain.

The inclined plane test has been used to evaluate integrated muscle function and strength in rodents by evaluating their ability to maintain body position on a board as its angle of inclination is increased.[30–38] This assessment method has been used routinely in models of spinal cord and traumatic brain injury to clearly quantify the functional deficits due to major trauma to the central nervous system.[32–38] In addition, the incline plane test has been shown to have specificity and sensitivity to distinguish between mild, moderate, and severe injuries and to track recovery of function over time.[34,37] This functional testing method has added utility since it does not require an extensive training period or motivation tactics (i.e., reward) and is simple, straightforward, and inexpensive. Although this method has been used extensively to evaluate motor deficits and strength in traumatic injury models, its utility for evaluating behavioral function in less-severe injury models of clinical conditions with motor impairments has been limited.

The purpose of this study was to extend the use of the incline plane functional assessment in two pain models of mechanical trauma in the neck to evaluate its utility for milder trauma injuries and to assess motor function outcomes. We implemented a modified incline plane test in models with well-defined development of behavioral hypersensitivity from two different tissue injuries in the cervical spine: a facet joint distraction (FJD) injury that simulates a painful whiplash injury and a nerve root compression (NRC) that induces sustained radiculopathy. We hypothesized that the baseline, uninjured performance on the incline plane test would be repeatable and that this assessment tool would be sensitive enough

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to distinguish differences between the different injuries. We further hypothesized that because the clinical literature suggests that radiculopathy is only sometimes associated with functional loss and a dorsal nerve root injury is not expected to affect function, that functional deficits associated with radiculopathy would be less-robust and/or not sustained. Accordingly, the performance of all rats for each injury and their matched Sham groups was measured repeatedly during a baseline period before surgical exposure and at time points following surgery that correspond to the time points when mechanical allodynia is established (day 1) and later when it still remains (day 7).

MATERIALS AND METHODS

All experimental procedures were performed using male Holtzman rats and were approved by the University of Pennsylvania Institutional Animal Care and Use Committee. Rats were housed under USDA- and AAALAC-approved conditions with free access to food and water. Rats underwent either a C6/C7 FJD ($n = 5$) or a transient compression of the C7 dorsal nerve root (NRC; $n = 5$); separate sham groups were also included for each model to control for the effects of surgery (FJD-sham, $n = 3$; NRC-sham, $n = 4$). In all rats, motor function was assessed prior to surgery and again on days 1 and 7 after surgery. At the start of studies, rats in the NRC groups weighed 250–300 g, and the FJD groups had larger weights (350–400 g) to accommodate the customized injury device for that model.[19–21,22–25] All procedures were performed under inhalation anesthesia (4% isoflurane for induction, 2% for maintenance). Surgical procedures for imposing NRC or FJD and shams were previously described.[20,21,23–25] FJD-sham procedures involved attachment to the loading device but no distraction was applied across the joint.[19–21] Procedures for NRC-sham were the same as its surgery with nerve root exposure via laminectomy but no compression.

Motor function was evaluated using a modified inclined plane test.[32,33,35] Accordingly, the inclined plane test was modified to be executed as a decline, with motor function measured by monitoring rodents' ability to support their own weight when placed facing downward on a board that is raised with increasing angle until they can no longer support their positioning. For these studies, the surface of the board (60 cm $\times$ 58 cm) was covered with a grooved rubber mat and had 10 cm high walls enclosing the surface on all sides except for the hinged edge. Each rat was placed on the board with its head facing down the slope of the incline to ensure that support of body weight would be sensitive to forelimb strength in this set-up.[34] For each trial, the board was initially inclined to 30° to reduce the rat's spontaneous movement at the start of the test.[36,39] The angle was increased at a rate of 2°/s until the rat was unable to maintain its position on the board. The maximum angle in each trial was recorded when one or both of the forepaws first slipped and were no longer able to maintain the initial body position. Trials in which the rat turned its body uphill without any limb slipping were not included. On any test day, three trials were performed for each rat, and the average angle taken as the response for that day. Baseline testing was performed on each of 3 days prior to surgery; following surgery, rats were evaluated for functional performance on days 1 and 7.

The repeatability of the decline angle board test for cervical assessments was evaluated using a two-way repeated measures mixed general linear model (GLM) to assess the effects and interaction between the injury groups and performance over the three baseline testing days. Intraclass correlation coefficients [ICC (2,1)] were calculated to evaluate the within-day repeatability of the incline board test for all animals.[40] Based on the repeatability analysis, the overall baseline value used in subsequent analysis and comparisons was calculated as the average of all three trials on the 2nd and 3rd baseline days. To compare the temporal performance responses in the incline board test between injury and sham groups, separate analyses were performed for the NRC and the FJD groups, with a two-way mixed GLM with repeated measures on one factor (time) used to evaluate any differences. Significant pair-wise differences were tested using Bonferroni's adjustment for multiple comparisons.

RESULTS

The rats used for the injury models had significantly different ($p < 0.0001$) weights, with the FJD group (398.8 $\pm$ 18.2 g) weighing more than the NRC group (317.8 $\pm$ 19.2 g) on the day of surgery. The mean baseline board angle (45.8 $\pm$ 3.1°) for the FJD rats was significantly greater ($p = 0.014$) than that for the NRC group (43.5 $\pm$ 2.5°; Fig. 1). The baseline values for both groups did not significantly vary over time (time effect, $p = 0.3584$) nor did the groups vary differently over time (group $\times$ time interaction; $p = 0.9943$; Fig. 1). Within-day ICCs for all rats were 0.237, 0.673, and 0.646 for the 3 consecutive baseline days, respectively.

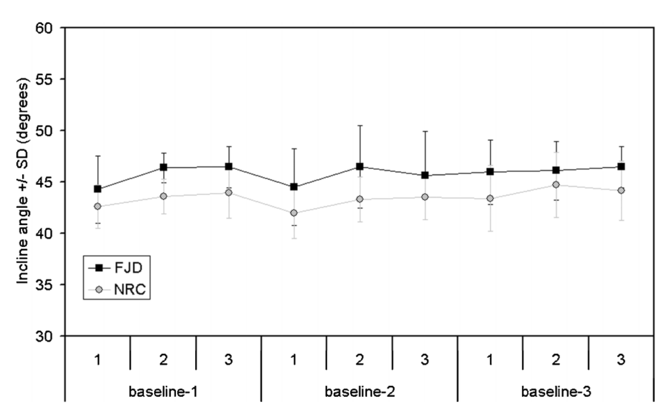

Figure 1. Mean incline angle for the baseline, unoperated responses for each group designated for facet joint distraction (FJD) and nerve root compression (NRC) procedures. Baseline testing consisted of three trials (1, 2, 3) on 3 separate days (baseline-1, baseline-2, baseline-3). The mean baseline incline angle for the FJD group was significantly higher ($p = 0.014$) than the NRC group.

Motor function responses were differentially induced for the two injury types. The injury × time interaction was significant ($p = 0.0049$) for the FJD group comparison (Fig. 2). For the FJD injury, motor function significantly decreased ($p < 0.001$) at day 1 compared to baseline and sham responses and remained lowered at day 7 (Fig. 2). Motor function was not significantly affected by FJD-sham procedures on either day 1 ($p = 0.22$) or 7 ($p = 0.48$) after surgery (Fig. 2). In contrast, only the time effect was significant for the NRC group comparisons ($p = 0.0016$). At day 1, slip for rats in both the NRC injury and NRC-sham groups occurred at significantly lower ($p = 0.0043$) incline angles compared to their corresponding baseline angles (Fig. 3). Yet, by day 7, performance in both groups had returned to baseline levels in both NRC groups (Fig. 3).

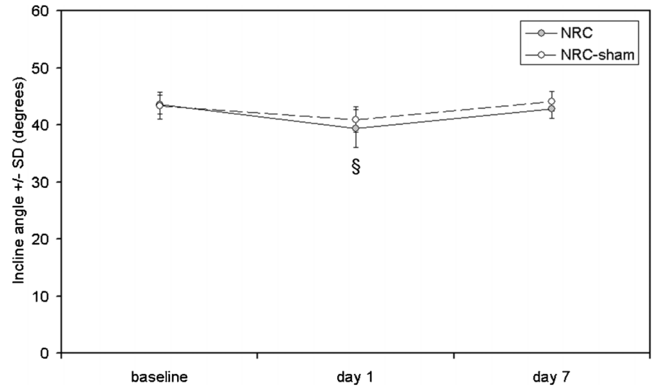

Figure 3. Mean incline angle for the nerve root compression (NRC) group. Both nerve root compression injury (NRC) and sham (NRC-sham) procedures produced a small, but significant ($^{§}p < 0.005$) decrease in incline board performance at day 1, but both groups returned to baseline levels on day 7.

DISCUSSION

The angle board test is a simple, objective, and sensitive method to assess motor function in models of painful neck injury (Figs. 1–3). Based on the ICCs (0.237, 0.673, 0.646), this study showed good consistency and reproducibility over the 3 baseline test days after 1 day of baseline testing. Both models induced sustained pain symptoms well-beyond the time points evaluated in the current study, with the responses to NRC being more robust and longer-lasting than the FJD.[22] Interestingly, the opposite trends were observed in performance on the incline plane test, with FJD producing sustained motor dysfunction at day 7, and the rats being able to support greater angles (Figs. 2 and 3). The painful NRC induced only an initial decrease in angle board performance that was recovered to baseline function by 7 days (Fig. 3). Although the lack of sustained impairment for the NRC is expected given that the injury involves only the dorsal nerve root, it is somewhat surprising given the surgical procedures in that model include a more-aggressive laminectomy to expose the root. In fact, disruption of the paraspinal musculature in both injury models may be responsible for some of the motor dysfunction, especially given reports of muscle and deep tissue hyperalgesia associated with pain.[26–29,41] This may explain the transient, but very subtle, deficit in function observed in both the NRC and NRC-sham at day 1 (Fig. 3).

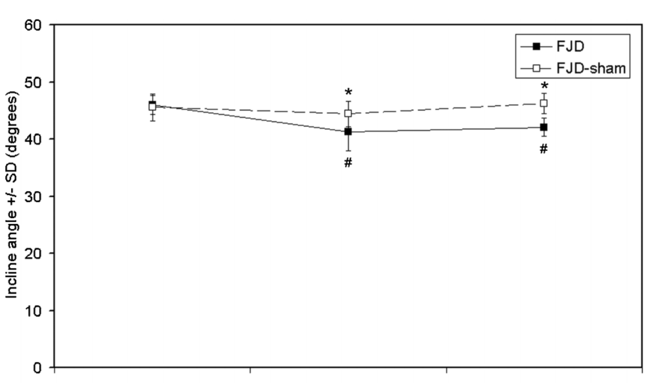

Figure 2. Mean incline angle resulting in slip for the facet joint distraction (FJD) group showing a significant, sustained decrease in motor function (lower angle) compared to sham (FJD-sham, $^{*}p < 0.001$) and baseline ($\#p < 0.0001$) on both days 1 and 7 post-surgery.

Ligaments, including the capsular ligament of the facet joint, are reported to monitor proprioceptive information and to activate the appropriate muscles to maintain joint stability.[42–44] In fact, distraction of the facet joint activates sensory afferents in the joint and increases muscle activity in the cervical spine.[45,46] Further, proprioceptive deficits, such as inaccurate perception of head position, were reported as secondary symptoms to whiplash injury in clinical studies.[47,48] Together, those experimental and clinical studies suggest that mechanoreceptors in the facet capsule that may be injured during its loading may modulate the activation patterns of the cervical spine muscles and result in more diffuse motor disturbances (Fig. 2) and pain. In contrast, in a model of inflammatory knee pain, the development of mechanical allodynia, and changes in gait parameters (paw contact with floor, paw print size/pressure) were not correlated.[49] However, direct injury to the sciatic nerve produced long-lasting gait changes concurrent with mechanical allodynia.[50,51] In a lumbar nerve root injury similar to that used here for the cervical spine, abnormalities in gait resolved within the first week while mechanical allodynia remained for up to 4 weeks,[52] which is consistent with our findings of only transient deficits in function but continued sensitivity in the radiculopathy model (Fig. 3).[22–25]

The baseline incline angles that initiated slip were significantly different for the groups of rats in the FJD and NRC groups (Fig. 1). Notably, the FJD rats maintained posture through a larger angle of incline, but had significantly greater body weights and were older than the NRC rats. Although the same strains of rats was used for this work, and all animals were sourced from the same supplier (Harlan Labs, www.harlan.com), the approximate ages of the rats were 54 and 75 days for the NRC and FJD groups, respectively, based on vendor data and body weights. The difference in these ages corresponds to differences in human populations that are analogous to the transition between juvenile and early adulthood (54 days) and that of adulthood (75 days), which may contribute to the observed differences in these two populations (Fig. 1). The age (or body weight) discrepancy could account for the different baseline responses for performance on the incline plane test. In fact, age-related changes in motor function were reported.[39,53] Murphy et al.[39] found that in evaluating motor function of rats with ages ranging from 2 to 29 months by the same methods as used in the current study, the 2-month-old group exhibited poorer function compared to the even the slightly older rats (5 and 9 months old). While those authors hypothesized that the sensorimotor systems required for the task were not yet fully developed in rats below 5 months of age,[39] such changes would not be manifest in the ages tested in our study. Further, the differential between ages in our study is at most only 2–3 weeks, so age may not be the major contributor to the changes observed in baseline responses (Fig. 1). Moreover, we did not evaluate the potential for relative differences in body mass to affect the outcomes. Coupling the observed differences between the two groups of rats having different body weights, with the age-related developmental issues, both of these factors may have contributed to the observed changes between groups (Figs. 2 and 3). Additional studies are needed with both models to better understand these and other changes that may contribute to functional differences.

The methods used to measure motor function generally followed those conventionally used to evaluate motor function in more severe trauma models.[30–32,34–37] However, modifications were made to implement this approach for our cervical models, including the positioning of rats facing downward on the board. This was done to help focus on the forelimbs for maintaining stability. In addition, unlike studies using gait analysis, the incline plane test cannot determine sided differences in responses as may be expected with the unilateral nerve root[30,49,52] Studies using additional behavioral assessment tools, such as grip strength, gait, and condition responses,[26–30,49,52] are needed to more fully define the extent and time course of motor function in these models of painful neck injury. Nonetheless, our results do support clinical observations that whiplash patients have impaired motor function associated with pain.

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