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CRITICAL REVIEW

Effectiveness of neural mobilization in patients with spinal radiculopathy: A critical review

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Summary Spinal radiculopathy (SR) is a multifactorial nerve root injury that can result in significant pain, psychological stress and disability. It can occur at any level of the spinal column with the highest percentage in the lumbar spine. Amongst the various interventions that have been suggested, neural mobilization (NM) has been advocated as an effective treatment option. The purpose of this review is to (1) examine pathophysiological aspects of spinal roots and peripheral nerves, (2) analyze the proposed mechanisms of NM as treatment of injured nerve tissues and (3) critically review the existing research evidence for the efficacy of NM in patients with lumbar or cervical radiculopathy.

Introduction

Nerve roots are susceptible to injury at any level of the spinal column, with a high percentage of these injuries occurring at the lumbar and cervical spine (Konstantinou and Dunn, 2008; Abbed and Coumans, 2007). Spinal radiculopathy (SR) is defined as a disorder of the spinal nerve root(s) most commonly caused by a disc herniation, or a space-occupying lesion that can result in nerve root inflammation, impingement, or both (Wainner et al., 2003). Also, malignant and infectious causes of SR have been reported and hence should always be suspected, as these patients would require medical referral and not any type of physiotherapy intervention (Stafford et al., 2007).

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Depending on the spinal level of nerve root irritation, SR can be further categorized as cervical (CR), thoracic (TR) and lumbar radiculopathy (LR). Epidemiological data for CR has shown an annual incident of 0.1% in males and 0.06% in females in the general population with an increased prevalence occurring in the fifth decade of life (Radhakrishnan et al., 1994). In the lumbar spine, the frequency of LR is highly variable, depending largely on the characteristics of the population studied, with annual values ranging from 2.2% in the general population to 34% in specific working populations (Konstantinou and Dunn, 2008). Men are more likely to have LR in their 4th decade of life, while women have higher rates in their 5th and 6th decade of life (Tarulli and Raynor, 2007). Thoracic disc herniation and diabetes mellitus are two of the most common etiologies for the development of TR. There is no available epidemiological data on TR, however certain data on thoracic disc herniations indicate that they occur in only 0.15—4% of all symptomatic disc herniations of the spine, and they represent less than 2% of all spinal disc surgeries (O'Connor et al., 2002). Since thoracic disc herniations are the less common across the whole spine and since disc herniation is the most common cause of SR (Radhakrishnan et al., 1994), TR should also be less common than CR and LR.

The pattern and location of the patient's symptoms may vary significantly, depending on the level of the affected nerve root (Cleland et al., 2005). The two most commonly affected levels are L4-5 or L5-S1 (90%) among all LRs (Murphy et al., 2009), and C7 (31%—81%), C6 (19%—25%) and C5 (2%—14%) among all CRs (Greathouse and Joshi, 2010). For TR, T11-T12 interspace is affected in 26%—50% of all cases (O'Connor et al., 2002). Common symptoms include weakness, numbness, paresthesia or a combination of all these symptoms (Young et al., 2009), which often cause disability and functional limitations (Cleland et al., 2005). SRs are often accompanied by (radicular) pain, but they are not defined by pain, as they can often occur in the absence of it (Bogduk, 2009).

Pathophysiology of injured nerves

In order to understand the mechanism through which any type of technique can have an effect on neural tissues, it is essential to understand the cascade of events that occur once a nerve has been affected by a mechanical or chemical stimulus that exceeds its threshold of tolerance.

Nerves have the ability to adjust to different types of mechanical stress imposed on them due to normal every day limb movements (Topp and Boyd, 2006). It is important for the integrity of the nerve that the duration and/or degree of the stress never exceeds the nerve's ability to withstand it. Ischemia and impaired function seem to be the first results when intraneural circulation and axoplasmic flow are blocked by compressive, tensile or shear forces (Topp and Boyd, 2006). Animal studies have demonstrated that nerves show time-dependent viscoelastic behavior (Topp and Boyd, 2006). Driscoll et al. (2002) investigated the effect of 16.1% strain on the sciatic nerve of 10 rabbits. They found that 16.1% of strain resulted in nerve blood flow reduction of 78% and that this reduction failed to recover after 30 min of rest. Jou et al. (2000) also found that 24% and 32% lengthening of the sciatic nerve of rats produced 50% drop in nerve blood flow measured with laser Doppler flowmetry. The effects of nerve compression, have also been extensively explored in animal models using various methods (miniature inflatable cuffs or silicon tubes around the nerve) to induce acute or chronic compression (Dahlin and Kanje, 1992; Dyck et al., 1990). Extraneural pressures have been found to inhibit intraneural microvascular blood flow, axonal transport and nerve function with increases of intrafascicular pressure in a dose—response manner (Rempel et al., 1999).

The main sources of compressive stress that will impede blood flow of the nerve root are disc herniations, osteophytes of the facet or uncovertebral joints and stenosis of the spinal canal (Kobayashi et al., 2003). With the contrary to dorsal root ganglion (Bogduk, 2009), root compressions can cause sensory and motor dysfunction but usually not pain (Mulleman et al., 2006). Pain, is typically generated when microvascular alterations as a result of compression lead to upregulation of inflammatory mediators (Kobayashi et al., 2004). Inflammation can ultimately lead to adhesions between the herniated disc and the nerve root that will impair gliding of the nerve root. In the acute and sub-acute stages of nerve root compression, neural conduction block, intraneural edema, mechanical sensitization and increase of sodium channel density have been reported (Chen et al., 2003; Kobayashi et al., 2004; Rempel et al., 1999). Dysfunction can also extend to primary sensory neurons within the dorsal root ganglion (Kobayashi et al., 2004). The result of these changes manifests itself as increased mechanosensitivity. It is worth noting that the critical threshold for duration and magnitude of compression has not been fully determined yet (Rempel and Diao, 2004).

Furthermore, substances contained in the herniated material can cause inflammation and radicular pain without evidence of true mechanical compression (Videman and Nurminen, 2004). This is because the nucleus pulposus is a very powerful inflammatory stimulus (Takahashi et al., 2003; Mulleman et al., 2006) possibly due to its high proteoglycan content (Urban and Roberts, 2003). Takebayashi et al. (2001), found mechanical hypersensitivity in the dorsal root ganglion of 14 rats after implanting nucleus pulposus at the L5 nerve root. In another animal study, induced neuritis in the sciatic nerve of rats produced axonal inflammation characterized by recruitment of macrophages and lymphocytes (Bove et al., 2003). This led to an increase of the pro-inflammatory cytokine, tumor necrosis factor alpha (TNFa), which in turn created spontaneous activity in nociceptors via an increase in sodium channel conductance. Elevated levels of neurotrophines such as nerve growth factor can sensitize C fibers of the nervi nervorum resulting in the release of prostaglandins and bradykinin (Onda et al., 2005; Greening, 2004). Other inflammatory mediators such as serotonin have also been involved (Kato et al., 2008). Interestingly, these inflammatory responses can cause nerve mechanosensitivity without evidence of major axonal degeneration and damage (Bove, 2008). Dilley et al. (2005) found that induced local neuritis in the nerve trunks of adult rats caused small numbers of structurally intact myelinated and unmyelinated afferent fibers to develop increased sensitivity to stretch and pressure. Patients presenting with radicular-like pain without radiculopathy (sensory and motor disturbance) are sometimes provided

with general diagnosis such as "non-specific neck and arm pain" or "cervico-brachial pain syndrome". Therefore, these diagnostic labels can include both radicular and referred pain. Given that SRs with inflammation only, without conduction problems closely resemble this clinical picture, studies that use these terms will also be reviewed.

Apparently, a mixture of compressive and inflammatory processes has a synergistic effect. There is evidence showing that, nerve injury is more pronounced when compression and chemical irritation present in combination than when each factor acts alone (Takahashi et al., 2003; Onda et al., 2005). Finally, as in any clinical pain state, insult to peripheral nerves will result in central sensitization with varying degree of severity (Woolf, 2011). In addition, it has been shown that nerve root irritation produces a stronger central response than peripheral nerve irritation (Greening, 2004).

Treatment

All three SR have a good prognosis and non-operative treatment is the appropriate initial approach (Kuijper et al., 2009; Stafford et al., 2007). Various interventions (manual therapy, traction, exercise and electrotherapy) have been proposed for cervical and lumbar radiculopathy and have been further scrutinized in systematic reviews (Clarke et al., 2010; Hahne et al., 2010; Boyles et al., 2011). However, there is still a need for additional high quality trials that will allow firmer conclusions on the effectiveness of these interventions (Hahne et al., 2010).

Neural mobilization (NM)

Different techniques that aim to mobilize the peripheral nervous tissue or its surrounding structures have gained considerable attention among therapists and researchers collectively known as NMs. These techniques are used by therapist for assessment and treatment of various compression syndromes as well as other conditions that may or may not involve neuropathic pain such as lateral epicondylalgia (Vicenzino, 2003). They involve a specific sequence of joint movements in which the therapist lengthens the nerve at one joint and simultaneously reduces its length at an adjacent joint in order to produce sliding movements of neural structures relative to adjacent tissues. These are known as sliders or gliding techniques (Shacklock, 2005; Butler, 2000). A slightly more aggressive maneuver is a tensioning technique which increases the distance between each end of the nerve tract in an oscillatory fashion (Shacklock, 2005; Butler, 2000). In addition, other techniques that produce an opening action around the nerve root such as dynamic and static opening of the bony and fascial interface (e.g. lateral glides) (Shacklock, 2005; Elvey, 1986) have been proposed for reduction of nerve root mechanosensitivity. Advocators of NM suggest that these techniques can be utilized to potentially rehabilitate normal function of the nervous system (Nee and Butler, 2006). So far, it has been shown that these techniques produce different amounts of longitudinal nerve excursion and strain, in both in vivo (Coppieters et al., 2009) and cadaver studies (Coppieters and Butler, 2008; Coppieters et al., 2006). Assessment of nerve mobility in relation to joint range of movement has also been explored (Herrington, 2006), as well as the effectiveness of NM in various types of peripheral neuropathies by means of improvement in pain (Tal Akabi and Rushton, 2000; Nagrale et al., 2012; Coppieters et al., 2003b) and motor nerve conduction velocity (Ha et al., 2012).

McKeon and Yancosek (2008) conducted a systematic review to assess the effectiveness of NM techniques for the treatment of carpal tunnel syndrome. NM showed only a positive trend towards improvement. In another systematic review, (Ellis and Hing, 2008), the therapeutic efficacy of NM in various musculoskeletal disorders such as low back pain, carpal tunnel syndrome, cervicobrachial neurogenic pain and lateral epicondylalgia was examined. Ten RCTs were included and the majority of these showed significant benefit after the application of NM techniques. Nonetheless, the authors in both reviews concluded that evidence for the efficacy of NM must be considered as limited due to methodological quality of the trials. They suggest that future studies should use more homogenous study designs, populations and pathologies.

Mechanisms of neural mobilization

Although several cadaveric, animal and in-vivo studies have been conducted in order to decipher the plausible mechanisms underlining the effectiveness of NM, the proposed explanations remain largely theoretical.

In a recent study by Brown et al. (2011), researchers examined whether the application of NMs on the tibial nerve in cadavers could have any effect on the simulated intraneural edema of the nerve. The results showed that passive NM induced a significant increase in fluid dispersion of the tibial nerve and could thus possibly explain how these techniques can prevent or reduce intraneural edema. Similar results are expected to be seen in living humans with peripheral nerve or root involvement although this should be evaluated in future studies (Brown et al., 2011).

The ability of NMs to induce hypoalgesia has been investigated. Beneciuk et al. (2009), found that a specific tensioning technique performed on the median nerve had an immediate hypoalgesic effect on C-fiber mediated pain, shown by thermal quantitative sensory testing on asymptomatic subjects. The authors suggested that the mechanism by which NM decreases thermal pain could be inhibition at the dorsal horn (Beneciuk et al., 2009). These positive results although informative are only short term and need to be validated with double-blind RCTs in symptomatic population.

In an animal study (Santos et al., 2012) researchers explored the effect of NM on chronic constriction model of sciatic nerve injury in 10 male rats. Immunohistochemistry and special protein analysis tests were used in order to measure nerve growth factor (NGF) and glia fibrillary acid proteins (GFAP) in the dorsal root ganglion and spinal cord of the animals. This was supplemented with assessment of allodynia and thermal and mechanical hyperalgesia. With the completion of 10 treatment sessions, researchers found a decrease of NGF and GFAP in the dorsal root ganglion and decrease of GFAP in the lumbar spinal cord along with associated reduction of allodynia and hyperalgesia in the experimental group. Although the results should be

interpreted with caution, findings from this study provide preliminary evidence that NMs can have an effect on inflammatory mediators involved in nerve pain.

In another animal study (Bertolini et al., 2009), researchers divided 23 rats with experimentally induced sciatica in three groups, receiving either dynamic or, static stretch of the sciatic nerve or sham treatment for 5 sessions. Pain was assessed with the use of a functional incapacitation test that measures paw elevation time during gate. Rats in the NM group showed lower paw elevation time and therefore greater reduction in pain compared to the static stretch and the sham group. Authors explained their findings in terms of reduced edema and intraneural adhesions which result in restoration of nerve mechanosensitivity.

Neural mobilization in cervical radiculopathy

In a prospected observational cohort study (Murphy et al., 2006), a multi-faceted treatment approach was applied in 27 patients with CR. Treatment was tailored to each patient and only those techniques that were deemed appropriate after thorough assessment were used on each patient. Modalities used in this study were cervical manipulation, over the door traction, end range loading maneuvers and NM directed to the affected nerve root. In the 3 months follow up, 25/27 patients reported clinically significant improvement in pain and disability. Despite the positive results, this study design does not allow any constructive conclusion on the effectiveness of NMs in isolation.

Ragonese (2009), carried out a randomized trial comparing manual therapy (cervical lateral glides, nerve glides, thoracic mobilizations) against therapeutic exercise (deep neck flexor, trapezius and serratus anterior strengthening) or a combination of both in 30 patients with CR. Inclusion criteria for CR was based on 4 examination findings (positive Spurling test, positive upper limb tension test, positive distraction test and ipsilateral cervical rotation less than 60°). The group which received the combination of exercise and manual therapy demonstrated the greatest improvements in terms of pain and disability after 9 treatment sessions in 3 weeks. Although the researcher used a small sample size of patients with CR, results demonstrate an additive effect on pain when NMs complement therapeutic exercises.

A recent randomized controlled trial, conducted by Nee et al. (2012) used 60 patients with nerve related neck and arm pain who were randomized in two groups receiving either NMs (lateral glides, nerve glides) with manual therapy and education or advice to remain active alone. Participants were excluded if they presented with two or more abnormal neurological findings at the same nerve root level or were suspected to have myelopathy or other red flags. Patients in the experimental group showed immediate, clinically relevant benefits after only 4 treatment sessions without any adverse effects related to the application of NM. This was the first randomized controlled trial that used a between group analysis in order to assess the effectiveness of NM in the short term. It is worth mentioning, that the inclusion criteria for this study population was based on a positive response to the application of upper limb neurodynamic test 1. This test does not inform the clinician of the specific site of nerve injury, but suggests increased mechanical sensitivity. Based on this, it is difficult to determine whether symptoms were due to nerve root irritation or any other dysfunction along the nerve tract.

In another pilot study (Allison et al., 2002), the authors randomly allocated 30 patients with cervico-brachial pain syndrome in three groups to receive either manual therapy with a focus on articular tissues of the shoulder and thoracic spine, NM techniques (lateral glides) or no treatment. Pain scores showed significantly lower values in the NM group compared to the other two groups. Similarly to the previous study, the term "cervico-brachial pain syndrome" is a rather general term that can include other peripheral nerve lesions apart from those of nerve roots.

Coppieters et al. (2003a) conducted a randomized clinical trial and divided 20 patients with peripheral neurogenic cervicobrachial pain in two groups to receive either NMs (lateral glides) or ultrasound. Inclusion criteria were based on certain clinical tests formulated by Elvey (1997) and included techniques of active and passive moment analysis, peripheral-nerve provocation tests and nerve palpation. Patients treated with NMs had significant changes for all outcome measures (ROM for elbow extension, symptom distribution, and pain intensity) immediately after the intervention compared to patients treated with ultrasound. Although there was no follow up in order to evaluate any sustained long term effects for NM, results indicate that NM has an immediate short term positive effect compared to ultrasound for patients with this type of neurogenic pain.

In one case study (Savva and Giakas, 2013), a slider NM technique was simultaneously applied on the median nerve with cervical traction, on a patient with CR. The patient reported improvement in all outcome measures including pain, and functional activities after 12 sessions spread over a period of one month. Although case studies can only inform evidence based practice to a limited extend, it is worth pointing out that this was the first study that used these two techniques (NM and traction) simultaneously. The rationale was that the cervical nerve root needs to be decompressed before mobilization is applied. Of course, larger, high quality randomized controlled trials must be conducted in order to validate the effectiveness of these two techniques combined.

Collectively, current evidence for the efficacy of NM techniques for patients with CR seems to be limited as only 3 studies have explored these techniques in patients with CR (Murphy et al., 2006; Ragonese, 2009; Savva and Giakas, 2013) and 3 studies in patients with nerve related neck and arm pain (Nee et al., 2012; Allison et al 2002; Coppieters et al., 2003a). NM techniques used in these studies mainly include treatment protocols as described by Elvey (1986). These follow the general principle of mobilizing tissues surrounding the nerve roots (nerve bed) in the acute phase followed by techniques directed at the neural tissue itself as mechanosensitivity decreases.

Neural mobilization in lumbar radiculopathy

Murphy et al. (2009), undertook an observational cohort study which applied a multimodal treatment approach, using a management algorithm depending on the patient's

symptoms. All 49 patients with LR were treated with a combination of manipulation, myofascial therapy and NM depending on the source of their symptoms on an individual basis. Each patient was seen 2—3 times per week for 3 weeks initially, after which they were reassessed. This was followed by either continued frequency of 2 times per week or a reduction in frequency to 1 time per week. The mean number of treatments was 12.6, with a mean duration of follow up after the end of treatment of 14.5 months. Approximately, 90% of patients reported an "excellent" or "good" outcome and more than 70% of patients had a clinically meaningful improvement in disability. In addition, 74% of patients reported meaningful improvement in pain and these improvements were maintained 14.5 months after the end of the treatment. NM techniques were applied in all participants in an attempt to minimize adhesions in the involved nerve root. The study was conducted in a single practice setting with a relatively small sample size, and without a control group. In addition, during the 14.5 months follow up, natural history could be credited for some of the improvement. Nevertheless, its findings are promising despite the fact that the beneficial results cannot be attributed to NM alone.

In contrast to the previous study, Scrimshaw and Maher (2001) randomly allocated 81 patients with LR that had undergone spinal surgery (lumbar discectomy, fusion or laminectomy) into two groups, one receiving standard postoperative care and the other group standard postoperative care plus NM. The results after 12 months of follow up indicated that NM did not offer any additional benefit to standard care alone. Nevertheless, it is important to underline that Patients demonstrated normal straight leg raise test. NM could have been more effective for these patients if their SLR, indicated increased neural mechanosensitivity. In addition, this study is the only one in post-surgical population, and the effects of surgical trauma in central nervous system mechanosensitivity makes interpretation of the results more complicated.

Schafer et al. (2011), carried out a prospective cohort study in an attempt to explore whether pain and disability differ in sub-groups of low back and leg pain treated with NM. The researchers proposed a pathomechanism-based system of evaluation which consisted of four categories: (1) patients with neuropathic sensitization, (2) patients with denervation, (3) patients with peripheral nerve sensitization and (4) patients with musculoskeletal pain. NM was utilized on 77 patients divided into one of these four groups following a standardized assessment protocol. After seven treatments with NM techniques, twice per week, the authors found that a significantly greater proportion of patients (56%) in the peripheral nerve sensitization group had a positive response to NM compared to the other three groups. According to the authors, LR would be included in the denervation group that did not show a favorable outcome after treatment with NM. The authors argued that NM is not the technique of choice for LR, since an NM technique would further stress an already compressed, hypoxic and oedematous nerve root and thus aggravate patient's symptoms. However, they do not comment on the positive effect of NM on peripheral nerves that can also be compressed, hypoxic and oedematous. Whether this difference can be explained by the lack of perineurium in nerve roots (Sunderland, 1990) is difficult to discern.

In addition, one randomized clinical trial (Nagrale et al., 2012), one pilot clinical trial (Cleland et al., 2006), one case series study (George, 2002) and two case studies (George, 2000; Cleland et al., 2004), also reported favorable changes in symptoms. Oddly enough though, all five studies excluded patients with LR assuming that participants who lacked nerve root involvement had a less severe condition and thus were more likely to respond to NM.

Discussion

Viewed in concert, results from available studies point toward a trend favoring NM techniques for SR but remain far from conclusive. Up to this point there are several reasons why we cannot reach any definite conclusions on the effectiveness of NM on patients with SRs:

1) Existing research literature lacks well designed RCTs that could clarify the effect of NM in SRs. Available clinical trials and case studies have small sample sizes, while most of them use a multimodal treatment approach that deprives us conclusive evidence of NM effectiveness in isolation.
2) Heterogeneity among studies seems to be a reason why it is so difficult to identify which treatment is most likely to be beneficial in which patient group. Chaitow et al. (2004) stress that if clinical trials wrongly assume that a large patient population is homogenous, they would fail to show clinical efficacy for specific interventions favorable for a certain smaller sub-group. A stratified approach by use of prognostic screening has been shown to be more effective than non-classification management (Flynn et al., 2002; Hill et al., 2011). Classification systems like the one proposed by Schafer et al. (2009) are on the right track for identifying which patient sub-group is more likely to respond to NM.
3) Definitions used across studies in order to describe pathology are non-specific and can include a range of different neurogenic and somatic disorders. For the medical community and pain scientists who are familiar with terms like radiculopathy and radicular pain, labeling such as "cervico-brachial pain syndrome", "non-radicular low back pain" or "non-specific neck and arm pain" is misleading and can create confusion. Sub-grouping patients in a distinct diagnostic group according to the unique mechanism/cause of their nerve injury (aetiological sub-grouping) (Wand and O'Connell, 2008; Schafer et al., 2009) could help reduce definition heterogeneity.

From the evidence presented, radicular pain in SRs seems to emerge from a complex interaction of inflammatory, immune, compression and central processes. For instance, proteoglycans from disc nucleus have been shown to provoke inflammation when they come in contact with nerve roots (Lee et al., 2006; Kawakami et al., 1999; Kayama et al., 1996). NO which is considered responsible for mediating this inflammatory response (Brisby et al., 2000) is also believed to activate glial cells in the area of

spinal cord and DRG in cases of neuronal damage (Watkins and Maier, 2005). Activated astrocytes and other glial cells contribute significantly in cytokine production and sensitization of pain transmitting cells in the dorsal horn of the spinal cord (Watkins and Maier, 2005; Tsuda et al., 2005). Prolonged pain due to inflammation as well as the synergistic action of glial derived growth factors and cytokines, cause memory type changes (long term potentiation) in the synapses of the spinal cord, thalamus and the brain collectively called central sensitization (Costigan and Woolf, 2000; Ji et al., 2003). When deciding to implement NM as an intervention, meticulous evaluation should be performed for signs of abnormal CNS sensitivity (e.g hyperalgesia, allodynia) as the response to mechanical treatments such as NM is expected to be limited.

With regards to compression related SRs, an important factor to consider is the duration of the compression. Sustained mechanical compression may in the long term cause injury to neurons of the dorsal root ganglion (Kobayashi et al., 2004), and damage to nerve axons, changes that are considered irreversible and thus unlikely to respond to NM treatment. Also, when presented with periradicular fibrosis and scarring, the nerve root will be fixed in one position and thereby applying mechanical force via any kind of neural movement based technique will only increase the susceptibility of the nerve root to reinjury (Kobayashi et al., 2009, 2003). In this clinical scenario, interventions that aim at reducing compressive pressure of the nerve root such as traction (Umar et al., 2012; Joghataei et al., 2004), foramina opening techniques (Shacklock, 2005) or lateral glides (Coppieters et al., 2003a) would appear to be more reasonable.

Patients with nerve sensitization due to inflammation in the absence of detectable nerve damage have been considered as a distinct category which is highly likely to respond to NM treatment. Examination procedures for identifying these patients have been proposed (Nee and Butler, 2006; Hall and Elvey, 2004) and include neural tissue provocation tests, palpation of nerve trunks and clues from specific pain provoking postures or activities. Overall, sensitivity, specificity and validity of this examination scheme has yet to be established, although studies have shown good inter-rater and intra-rater reliability for certain neural tissue provocation tests (Vanti et al., 2010; Jespen et al., 2006) and promising results from a proposed classification system (Schafer et al., 2009). Patients more likely to respond to NMs are those who demonstrate improvement of symptoms with techniques, positions or movements that increase the size of the intervertebral foramen, and show no or limited psychological comorbidity and/or signs of abnormal CNS sensitivity.

On the other hand, trying to differentiate nerve pain due to inflammation with intact nerve axons, from traumatic neuropathic pain with true axonal damage, by using movement based screening techniques, has been questioned (Zusman, 2008, 2009). To date, this distinction is based on screening patients with cardinal signs of nerve axonal damage such as pain distribution, decreased reflexes, and motor and sensory deficits (Stafford et al., 2007). Also, it is cautionary to consider that nerve root inflammatory pain might evolve to become neuropathic pain or even a mixture of both (Zusman, 2008). In addition, central mechanisms of pain should always be taken into consideration and carefully assessed, since both central and peripheral mechanisms interact (Nijs et al., 2010). It is reasonable to postulate that SR patients with dominant, hard-to-treat central sensitization that includes maladaptive psychological factors such as negative emotions (depression, anxiety), cognitions (catastrophizing, external locus of control) and pain behaviors (fear of movement, fear of reinjury, avoidance of activity) (Zusman, 2002; Woolf, 2011), would not be appropriate candidates for NMs that essentially target peripheral pain mechanisms (Schafer et al., 2011). Such maladaptive emotions, cognitions and behaviors can be screened via a combination of questionnaires such as Tampa Scale of Kinesiophobia, McGill Pain Questionnaire, Beck Depression Inventory and others (Lebovits, 2000). In those cases a more hands off, pain management and cognitive-behavioral approach is recommended by the authors even in the presence of physical trauma.

In conclusion, since there has been considerable evidence from animal models showing that nerve root inflammation can be present with functional (e.g. mechanosensitivity) but not structural nerve root deficits, it should be of interest if future studies can ascertain whether these basic science findings could then be incorporated into clinical practice. This would allow adequate screening and classification to take place, in order to determine the efficacy of NM on this discrete sub-group of patients. With these improvements in future studies and the integration of basic and clinical research related to NM, there will be immense progress in clinical decision-making and management of SRs.

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