International Journal of Neurology and Neurosurgery
Volume 4 Number 4, Jul - Dec 2012

Role of Sympathetic Nervous System in Pain: Mechanism-Based Examination and Treatment using Physical Therapy: A Focused Review

Ketaki C. Joshi*, Senthil P Kumar**

Abstract

Musculoskeletal pain (MSKP) was proposed to arise from various mechanisms out of which nociceptive mechanism was common. Role of Sympathetic nervous system (SNS) in MSKP was not recognized until stress was found to have effect on MSKP. Thus this review focuses on the role of SNS in MSKP and its evaluation and treatment.

Recent studies have suggested that SNS contributes to chronic pain. It forms the secondary component of pain dysfunction. This type of pain was termed as 'Sympathetically Maintained Pain' (SMP). It can occur due to a pathophysiological or pathomechanical cause. Various mechanisms have been proposed for SMP based on animal and human studies. It has been proposed that sympathetic- sensory coupling is responsible for SMP. Sympathetic- sensory coupling can occur directly in dorsal root ganglia, chemical coupling in the skin, or development of alpha adrenoceptor mediated supersensitivity. The mediator for the coupling is nor-adrenalin and the adrenergic receptors involved are the alpha 2 adrenoceptors. Diagnosis of SMP is based on signs and symptoms, routine physical examination, specific neurodynamic tests like Sympathetic Slump test, and sympathetic blockade. SMP is managed using pharmalogical treatment and physical therapy. Thus, SMP presents as a true clinical challenge and key to successful management is early diagnosis and treatment.

Keywords: Sympathetically maintained pain; Chronic pain; Sympathetic nervous system; Musculoskeletal pain; Sympathetic slump.

Introduction

Musculoskeletal pain (MSKP) was proposed to arise from five mechanisms- nociceptive, peripheral neurogenic, central neurogenic, cognitive-affective and sympathetic[1]. Patients with MSKP presents with multiple mechanisms in operation with relation to their pain and other complaints though nociceptive mechanism was more common, other mechanisms were also equally prevalent[1]. The role of sympathetic nervous system (SNS) in MSKP was not much recognized until stress and its effects on musculoskeletal system was elucidated. Stress bears a direct effect on SNS by inducing sympatho-excitation and activation-response leading to increased production of adrenaline and noradrenaline by an endocrine gland- the adrenal medulla.

It is not uncommon to observe local changes in the part with MSKP, an abnormal vasodilatation or constriction, colour changes, texture changes and sweating abnormalities. However, therapists for long and commonly relied on nociceptive mechanism for treating MSKP[2] and authors advocated emphasis on missing mechanisms such as cognitive-affective in therapists' understanding of patient symptoms and clinical decision-making[3].

SNS has the potential not only to initiate an immediate protective response to an actual or perceived injury/threat, but also react on a

Author's Affilation: *Physiotherapist, Thakar's Physiotherapy Clinic; 16, Gurudev Basement- A, Suryodaya chs, Near NIIT, Opp Railway Atation, Ambernath (E) 421 501, Thane Dist, Maharashtra, **Associate Professor in Musculoskeletal and Manual Therapy, PhD Candidate, Dept of Physiotherapy, Kasturba Medical College (Manipal University), Mangalore.

Reprint's request: Senthil P. Kumar, Associate Professor in Musculoskeletal and Manual Therapy, PhD Candidate, Dept of Physiotherapy, Kasturba Medical College (Manipal University), Mangalore. Email: senthil.kumar@manipal.edu

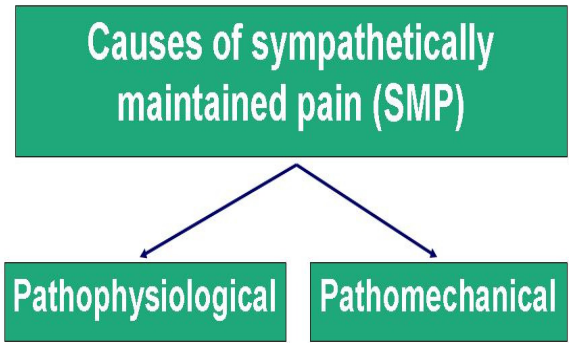
(Received on 05.06.2012, accepted on 17.07.2012)

longer term through its inherent anatomical and physiological inter-relationships with central nervous system and the endocrine system. Understanding of SNS and its role in MSKP is thus essential for physical therapists evaluating and treating patients with MSKP. The objective of this review is to update the professional community on the importance of SNS in MSKP, its evaluation and treatment based upon established evidence from current literature.

Background

The Sympathetic Nervous System (SNS) is the larger of 2 divisions of the autonomic nervous system (ANS). It is mostly an efferent system. SNS innervates many peripheral structures and affects many bodily functions via á and â adrenoceptors. Recent studies have suggested its contribution to chronic pain[4]. A full blown syndrome of sympathetic system dysfunction is easy to recognize, but it can also present in a more subtle and limited way[5]. Only a local area may be painful, and there may be no colour changes or sweating. Even this mildest form of sympathetic system dysfunction may be associated with substantial functional loss. Therefore, early diagnosis and treatment of sympathetic dysfunction is very important. If not recognized, mild sympathetic system dysfunction can progress to full blown syndrome. Lack of rehabilitation can further lead to poor compliance and added emotional stress.

Figure 1: Causes of sympathetically maintained pain (SMP)



Sympathetic system is a secondary component of pain dysfunction [5]. It is secondary because it is initiated by injury to non- sympathetic tissue. In 1986, Robert termed this type of pain as Sympathetically maintained pain (SMP) [5]. This terminology allows all painful sympathetic nervous system dysfunctions to be grouped under one heading and eliminates the need to describe these conditions by their confusing and often overlapping clinical signs and symptoms. Sympathetically Maintained Pain (SMP) is a special type of neuropathic pain. The pain component in patients with neuropathic pain which is relieved by specific sympatholytic procedures is considered as SMP and which is not relieved by sympatholytic procedures is considered as Sympathetically Independent Pain (SIMP). Thus SMP is defined to be a symptom and not a clinical entity [6]. SMP is defined as a pain that is attributable to a modification of sympathetic efferent function in peripheral tissues [7].

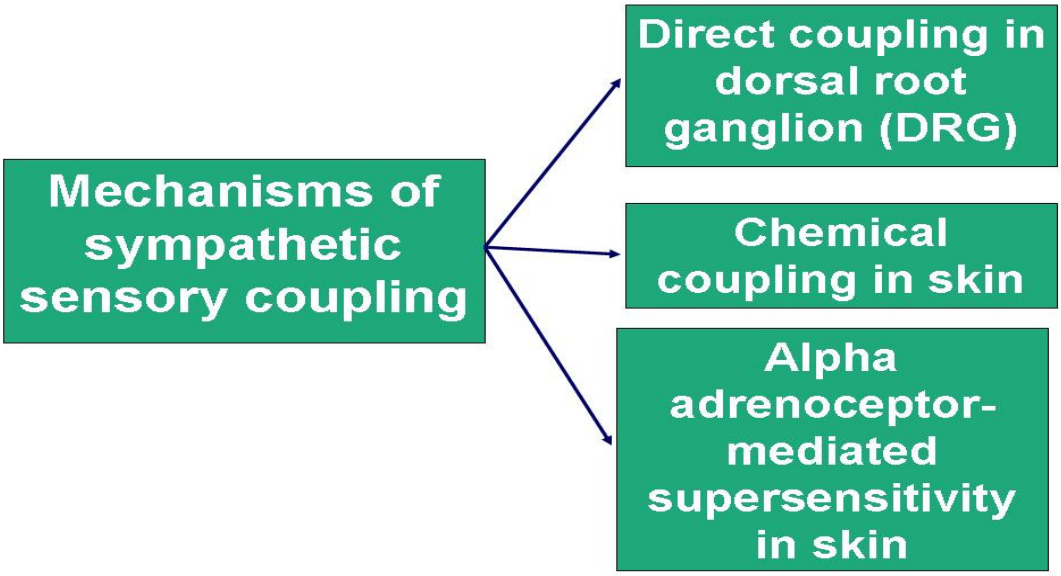
Causes

SMP can result either from a pathophysiological cause or pathomechanical cause (fig 1). pathophysiological causes can be complete or partial nerve injury or tissue inflammation. Pathomechanical cause can be distortion, stretch, or irritation of the sympathetic trunk, sympathetic ganglia and rami communicans which further leads to altered physiology via axonal transport mechanisms [4]. This type of mechanical dysfunction can occur during normal movements if sympathetic neural tissue mobility is impaired.

Mechanism

Injury to the musculoskeletal tissues influences autonomic nervous system via sympathetic dominance[8]. The stimulation of supraspinal sites facilitates spinal nociceptive transmission both of which produce

Figure 2: Mechanisms of sympathetic-sensory coupling



autonomic and behavioral effects. Long term activation of spinal and extra spinal nociceptive afferents causes stimulation of autonomic nervous system that may have deleterious effect on visceral function and homeostasis. Under physiological condition, primary afferent nociceptors do not have catecholamine sensitivity and their activity is unaffected by sympathetic outflow. But, under pathological conditions the sympathetic efferents enhance the primary afferent nociceptor activity[6].

The pathophysiological basis of SMP has shifted from sympathetic overactivity to model that incorporates sensitized polymodal nociceptors, sensitization of central nociceptive pathways in response to chronic nociceptive input, modulation of somatomotor and somatosympathetic reflexes and associated changes in sympathetic outflow and skeleto- motor outflow[7]. The influence of sympathetic neurons on afferent neurons can be distinguished into two categories depending on whether the coupling between afferent and sympathetic neurons occur due to traumatic nerve injury or peripheral tissue damage[9]. Catecholamines released by the sympathetic efferent nerves have been found to activate adrenoreceptors

Studies done on animals provide strong support for the concept of chemically mediated sympathetic –sensory neural coupling mediated by the alpha adrenergic receptors[10]. But the alpha adrenoreceptors subtype expression and function may differ between species and may be influenced by the site of injury. Human studies implicate nor-adrenalin in development of hyperalgesia in sensitized normal skin, either through direct binding or sensitization of alpha adrenoreceptors[10]. The nociceptive actions of nor- adrenalin are mediated by alpha 1 adrenoceptors in SMP.

The current hypothesis for sympathetic – sensory coupling is:1) direct coupling between sympathetic and sensory neurons in the dorsal root ganglion; 2) chemical coupling between the sympathetic and nociceptive neuron terminals in the skin; 3) development of alpha adrenoceptor- mediated supersensitivity in nociceptive fibres in skin in association with the release of inflammatory mediators (fig 2)[10].

Direct coupling between sympathetic and sensory neurons in the dorsal root ganglion

Peripheral nerve lesion triggers sympathetic nerve sprouting in the dorsal root ganglion. Newly sprouted post ganglionic sympathetic

fibres have been observed to form basket like structures around primary neuronal cell bodies that survive nerve lesion. Later it was found that long-term effect of increased activity was inhibitory and therefore unlikely to account for SMP. The proportion of DRG neurons responsive to nor-adrenalin increases markedly following chronic nerve injury. Similarly the proportion of the DRG neurons expressing the alpha 2a adrenergic immunoreactivity increases following complete or partial transaction of nerve.

Chemical coupling between the sympathetic and nociceptive neuron terminals in the skin

Studies also provide evidence that the alpha adrenoceptors may be constitutively expressed on some sensory fibres in the skin and their expression is upregulated following nerve lesion. Newly sprouted aberrant sympathetic fibres wrap around the sensory fibres forming novel associations that provide a histological substrate for chemically mediated sympathetic sensory coupling between sympathetic nerve terminals and sensory receptors. The mechanism of coupling might involve increased activation of alpha adrenoceptors.

Development of alpha adrenoceptor- mediated supersensitivity in nociceptive fibres in skin in association with the release of inflammatory mediators

Adrenergic responsiveness in not due to the exposure of alpha adrenoceptors to increased concentration of ligand but rather that decreased availability of ligand results in increased sensitivity and/or expression of the receptor. Receptor sensitization and changes in expression may be associated with tissue trauma and inflammation. Tissue trauma triggers release of wide range of inflammatory mediators like, bradykinin, histamine, prostaglandins, etc. Ectopic stimulation of nociceptive neurons can cause release of neuropeptides such as substance p and calcitonin gene related peptide (CGRP) which drives neurogenic inflammation. Sympathetic nerve terminals may further contribute to the pain and inflammation by enhancing the turnover of inflammatory mediators and substances like nerve growth factor and prostaglandins, or may directly trigger firing of nociceptive neurons by activating alpha adrenoceptors on nociceptive afferents. In the context of pain generation, the ultimate product is generation of a chemical soup of mediators that act synergistically to decrease the receptor threshold and amplify the receptor response. The adaptations occur via the changes in the expression of sodium channels, capasaicin sensitive channels, vanilloid receptors and temperature sensitive ion channels.

Finally, deafferentation may affect sympathetic output[5]. Constant and normal sensory input is thought to suppress sympathetic activity. In case of sympathetic pain, skin sensitivity causes the patient to minimize contact. This results in decrease in afferent activity which limits the normal inhibition of sympathetic system allowing increased sympathetic discharge. These can explain the positive clinical results seen with massage and desensitization of a body part affected by SMP.

Integrative hypothesis

Previous unpublished data demonstrate a close physical association between sympathetic neurons and sensory neurons in upper dermis of normal human skin and rat skin[10]. Previous study has suggested that the fibres of sympathetic and sensory neurons are in closed proximity to each other and appear to be interwined. This provides a pre existing histological substrate in which sympathetic-sensory coupling may occur under altered physiological conditions. Under altered conditions, alpha adrenoceptors associated with afferent nociceptive fibres may become increasingly sensitized or even fire spontaneously. Following nerve injury the inflammatory cells like macrophages accumulate at the site of injury and at proximal and distal sites. These close relationships may result in the exposure of the

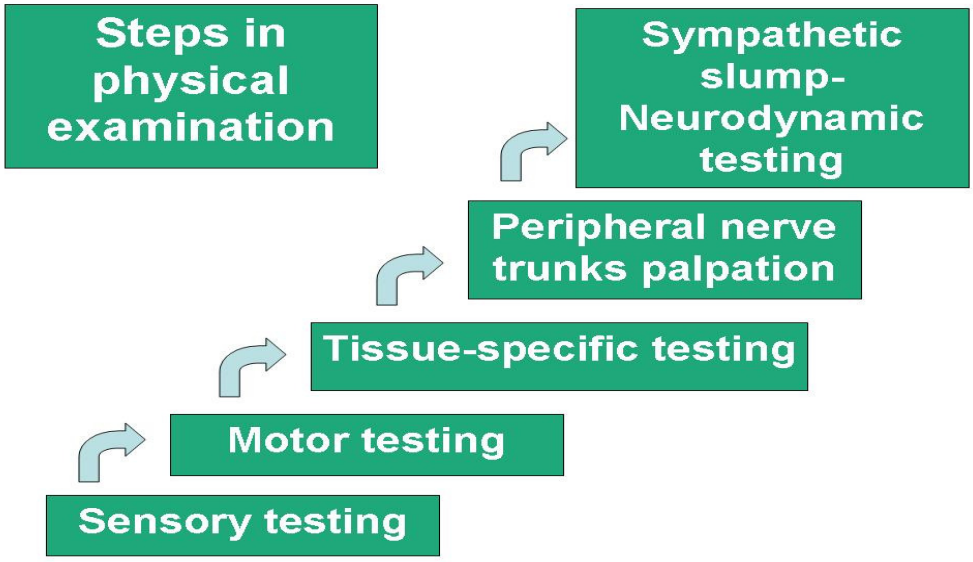
nociceptive axons to he sensitizing molecules secreted by the inflammatory cells. Macrophage releases nerve growth factor and induces other non- neuronal cells to produce nerve growth factor which in turn stimulates mast cell degranulation and release of prostaglandins, bradykinin, histamine, serotonin which sensitize the nociceptive afferents. Alternatively, inflammatory conditions induce changes that result in up regulation of alpha adrenoceptors on nociceptors. It is worth considering the possibility that alpha adrenoceptors are not expressed on the nociceptive fibres but on closely related cells that are capable of exciting the nociceptive fibres, such as Schwann cells. Glial cells also contribute to pain generation by releasing substances that excite neurons. It may also explain the unusual symptom expansion pattern experienced by many CRPS patients. Similarly, Schwann cells also exhibit property like gill cells and thus can be responsible for hyperalgesia in the skin. Finally, migration and sprouting of sympathetic fibres would contribute to the ongoing development of the histological substrate and to increased regional availability of noradrenalin.

Signs and Symptoms

- Follows a non- anatomical distribution.
- Pain may not involve a larger area or an entire extremity. Preganglionic neurons travel through several ganglia before synapsing on 4 to 20 post ganglionic neurons. Each spinal level may synapse with multiple peripheral ganglia that supply multiple targets. Such a feature is responsible for intrinsic ability of the SNS to exert widespread effects, on a number of targets.
- Pain is described as burning in nature.
- Pain is disproportionate to the injury.
- Earliest and most helpful sign of early sympathetic dysfunction- intolerance to cold.

In classic case, within first six weeks or after injury the sympathetic overreaction causes a swollen, immobile, and painful limb associated with increased sweating and colour changes in the extremity. Frequently there is allodynia, which is pain produced by a non- noxious stimulus such as light touch, hyperalgesia, which is overreaction to a painful stimulus. In later stages, there are trophic changes:

Figure3: Steps in physical examination



dystrophic, smooth and shiny skin, brittle nails, osteoporosis, muscular and subcutaneous atrophy. In chronic sympathetically maintained pain, patients may also present with extra- articular swelling and joint contractures.

Physical examination

Physical examination includes routine sensory tests, motor tests, target tissue examination and palpation (fig 3)[11]. Nerve palpation is performed to assess the peripheral nerve sensitivity. Changes include thickening, swelling, neuromas, neurofibromas, or alteration in sensitivity to palpation in peripheral nerves. Neurodynamic tests like, upperlimb neurodynamic tests, straight leg raise test, slump test are useful indicators of peripheral and central sensitization. Sympathetic Slump test is a test which specifically assesses the mobility of sympathetic trunk[11]. A Sympathetic Slump test that reproduces symptoms may indicate sensitivity of the peripheral SNS in response to dorsal root horn or sensitized target tissues. It does not implicate the sympathetic trunk as the cause of pain.

Investigations

Sympathetic blockade is the best method for diagnosis of sympathetically mediated pain[5]. If a complete sympathetic blockade does not relieve the pain, the disorder most likely is not SMP. One of the easiest ways to achieve sympathetic blockade is intravenous administration of alpha blocker such as phetolamine. This creates complete sympathetic blockade. But the blockade is for short duration thus cannot be used as a treatment technique.

Treatment

Treatment modalities include: sympathetic blockade, through either blocks or operative interruptions; pharmacological treatment for both sympathetic and non- sympathetic symptoms; and physical therapy. When SMP is diagnosed in early stages, repeated long lasting paravertebral blocks can be an effective treatment. Blocks can be given as frequently as every other day for 2 weeks to achieve long –lasting effect.

Pharmacological treatment

Pharmacological treatment cannot take place of early diagnosis and appropriate treatment with sympathetic blockade[5]. It is more commonly used to control the symptoms associated with chronic stage of the disease. Although not universally accepted as an effective treatment, oral corticosteroid may reverse early SMP. Non- steroidal anti-inflammatory can also be used to treat SMP. These drugs are cyclooxegenase inhibitors and interfere with production of prostanoids. The use of narcotics and benzodiazepines is not recommended as they lend to lead to drug dependence, depression, and increased pain.

Sympathetctomy is the procedure of last resort, if anaesthetic sympathetic blockade has provided good short term but not long term relief [5]. Although many patents have good early relief with lumbar sympathectomy, the symptoms tend to recur and after five years patients return to their pre treatment condition.

Physical therapy

It is important to understand that a patient with sympathetically maintained pain cannot be managed with normal post-operative care[5]. These patients have abnormal pain responses like allodynia, hyperalgesia. The therapist must have the patient progress slowly with exercises and not force the pace too vigorously. As these patients have intolerance to cold, moist heat is more effective for reducing pain and stiffness. The most important element for successful rehabilitation is the avoidance of personality confrontations[5]. Theses patients are frequently withdrawn, depressed, angry, and unwilling to co-operate with therapy because of pain and dysfunction. Therefore, personality defects should be assumed to be a

part of disease and not an integral part of patient.

Gentle reactivation and desensitization

Explanation should be given about what patient can do safely. Patient should be advised about limiting the nervous system stimulants including, caffeinated drinks and cigarettes. Desensitization can be done by advising the patient to play with materials that have different textures like, clay, sand, etc[11]. Gentle self massage within limits of mechanical allodynia and hyperalgesia can be done. Sensory program should be progressed by increasing the time and decreasing the temperature, and exploring more sensory options.

Isometric movement and flexibility

Aggressive range of motion activities should be avoided to minimize the proprioceptive input to an already sensitized dorsal horn[11]. Active or active assisted range of motion exercises should be encouraged. Transcutaneous electrical stimulation may be tried as a pain control measure during exercise. Hydrotherapy may be useful in early stage of management when weight bearing is provocative. Initially non- weight bearing exercises which load the affected area should be introduced and progressed to weight bearing activities interspersed with non-weight bearing activities.

Spinal manipulative therapy and Neural mobilization in SMP.

Recent studies of both symptomatic and asymptomatic individuals have reported that SMT produces an immediate hypoalgesic effect which is specific to mechanical nociception[12]. This hypoalgesia occurs concurrently with sympathetoexcitation. These findings of concurrent hypoalgesia and sympathoexcitation appear to be parallel effects produced by stimulation of dorsal periaqueductal gray area of midbrain (dPAG) in animal studies[12]. Thus, the pattern of symapthoexciation occurring concurrently with SMT may illustrate link between manual therapy techniques, dPAG and descending pain pathways[13]. Periaqueductal grey (PAG) is one of important centres in brain for endogenous control of pain. The connections from PAG to the intermediolateral horn of spinal cord facilitate autonomic changes in presence of stressors. Connections from the PAG to the dorsal horn mediate analgesia and

Figure 4: Sympathetic slump technique performed for left sympathetic trunk (with costo-vertebral mobilization)

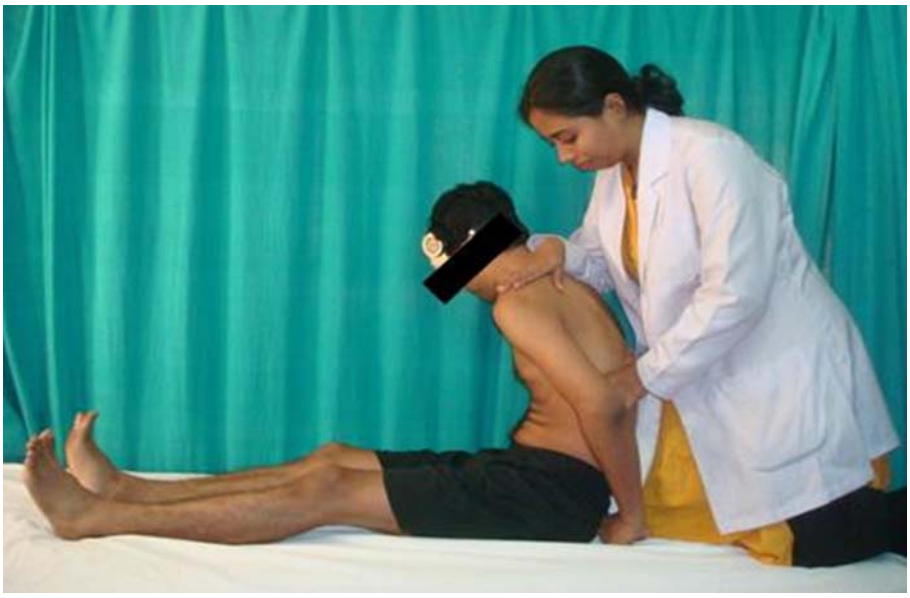
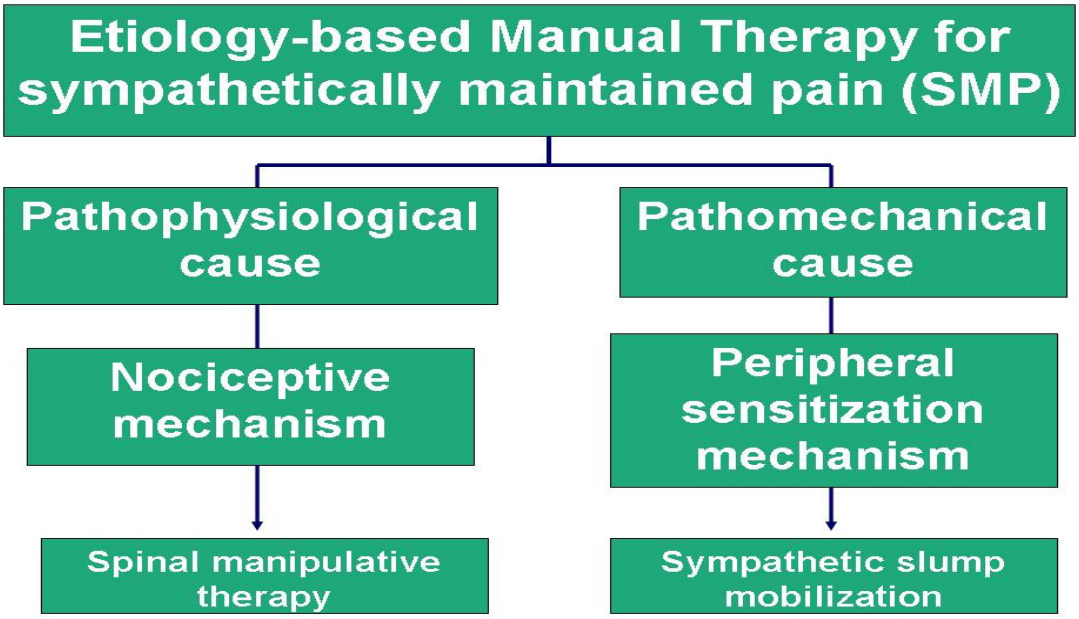


Figure 5: Schematic inter-relationship between aetiology-based and mechanism-based manual physical therapy management of sympathetically maintained pain (SMP)



influence motor activity to the anterior horn[11]. Analgesia from the dPAG (dorsal system) is described as being non- opoid and is associated with an immediate defense response in relation to stressful situations. The associated physiological responses are consistent with sympathetoexcitation and activation of alpha motorneurons at the spinal cord level. As the stress reduces the analgesia shifts from non-opoid to opoid analgesia via vPAG. This is associated with sympathoinhibition and depression of motor activity[11].

It is thought that the initial hypoalgesic effect of Manipulation induced analgesia (MIA) in normal subjects is mediated by the descending pathways from the PAG via nuclei in the ventrolateral medulla to the spinal cord[11]. From the investigations it appears that specific manipulative physical therapy techniques exert an initial sympathetoexcitatory effect (within 15 seconds) that is most significant during the treatment procedure. Data generated from the studies suggest that the initial sympathetoexcitatory effects of specific manipulation are associated with the mobilization of the descending pain-control systems in particular with the non- adrenergic system. As the associated hypoalgesic or analgesic effect is associated with this sympathetoexcitation is likely to be mediated via the descending noradrenergic pathways, it is classified as non-opoid.

The immediate sympathoexciatory effect has also been demonstrated in studies using neural mobilization. Neural mobilization produces greater changes in the measures of SNS than produced by accessory joint mobilizatio[14]. Previous studies have reported the physiological effects of Sympathetic Slump test on the measures of SNS. It was found to have sympathoexciatatory effect in upperlimbs and trend towards sympathoexciatory effect in lower limbs in asymptomatic individuals[4,7]. Also, Sympathetic Slump mobilization along with costovertebral mobilization was shown to be an effective treatment in patients with CRPS[15]. Sympathetic Slump is proposed to have specific effect on the sympathetic trunk. The sympathetic trunk lies exactly anterior to the costovertebral joints at the 10^{th}, 11^{th} and 12^{th} rib level. Thus, the costovertebral mobilization is given at 10^{th}, 11^{th}, and 12^{th} rib level [15]. Thus, Sympathetic slump may be effective treatment technique in patients with SMP. (fig 4).

Considering the mechanism by which SMT and neural mobilization has its effect on SMP, the management of SMP is classified depending upon the cause. SMT plays a major role in management of SMP with pathophysiological cause and Sympathetic slump can be used as an effective treatment technique for SMP with pathomechanical cause. (fig 5)

Conclusion

Thus, sympathetically maintained pain presents a true clinical challenge. As this condition frequently does not manifest all of its possible symptoms, the clinician should be aware of other findings such as intolerance to cold, allodynia that may be the only signs of SMP. The key to successful management is early diagnosis and treatment. The patience, concern and skill of the physical therapist and other health care professionals, working as a team is very important for successful outcome. As previous studies have shown that manual therapy techniques have specific effects on the SMP, further randomized controlled trials should be carried out to develop a better understanding of these manual therapy techniques on SMP and establish an etiological based classification for treating SMP.

References

1. Kumar SP, Saha S. Mechanism-based classification of pain for physical therapy in palliative care-a clinical commentary. *Indian J Palliat Care* 2011; 17: In press.
2. Smart K, Doody C. Mechanisms-based clinical reasoning of pain by experienced musculoskeletal physiotherapists. *Physiotherapy* 2006; 92: 171-8.
3. Smart K, Doody C. The clinical reasoning of pain by experienced musculoskeletal physiotherapists. *Man Ther* 2007; 12: 40-9.
4. Cleland JA, Durall C, Scott SA. Effects of slump long sitting on peripheral sudomotor and vasomotor function: a pilot study. *J Man Manip Ther* 2002; 10: 67-75.
5. Lindenfeld T, Bach B, Wojtys E. Reflex sympathetic dystrophy and pain dysfunction in the lower extremity. *J Bone Joint Surg* 1996; 78A: 1936-44.
6. Baron R, Raja SN. Role of adrenergic transmitters and receptors in nerve and tissue injury related pain. In: Malmberg A, Chaplan SR. *Mechanism and mediators of neuropathic pain*. Switzerland; Birkhauser, 2002; 153-174.
7. Slater H, Vicenzino B, Wright A. Sympathetic Slump: the effects of a novel manual therapy technique on peripheral sympathetic nervous system function. *J Man Manip Ther* 1994; 2: 156-63.
8. Grimm DR, Cunningham BM, Burke JR. Autonomic nervous system function among individuals with acute musculoskeletal injury. *J Man Manip Ther* 2005; 28: 44-51.
9. Janig W, Levine JD, Michaelis M. Interactions of sympathetic and primary afferent neurons following nerve injury and tissue trauma. *Prog Brain Res* 1996; 113: 161-84.
10. Gibbs G, Drummond P, Finch P, Phillips J. Unraveling the pathophysiology of complex regional pain syndrome: focus on sympathetically maintained pain. *Clin Exp Pharmacol* 2008; 35: 717-24.
11. Grant R. *Physical therapy of the cervical and thoracic spine*. 3rd ed. Churchill Livinstone, 1994; 295-319.
12. Sterling M, Jull G, Wright A. Cervical mobilization: concurrent effects on pain, sympathetic nervous system activity and motor activity. *Man Ther* 2001; 6: 72-81.
13. Moulson A, Watson T. A preliminary investigation into the relationship between cervical snags and sympathetic nervous activity in the upper limbs of an asymptomatic population. *Man Ther* 2006; 11: 214-24.
14. Simon R, Vicenzino B, Wright A. The influence of an anteroposterior accessory glide of the glenohumeral joint on the measures of peripheral sympathetic nervous system function in the upper limb. *Man Ther* 1997; 2: 18-23.
15. Cleland JA, McRae M. Complex regional pain syndrome I: management through the use of vertebral and sympathetic trunk mobilization. *J Man Manip Ther* 2002; 10: 188-99.