Are reviews based on sham acupuncture procedures in fibromyalgia syndrome (FMS) valid?

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Abstract

In recent reviews regarding the efficacy of acupuncture in fibromyalgia syndrome (FMS) it has been concluded that acupuncture has no specific effect since the control procedure (superficial needling and/or needling away from 'specific' points) had similar effects. These conclusions may be questioned since superficial needling and/or needling away from specific trigger points is not inert. Also, manual acupuncture or mild electroacupuncture (EA) may not be sufficient to activate the endogenous pain inhibiting system.

Patients with FMS suffer from allodynia, fatigue and muscle ache, which is partly explained by peripheral and central sensitisation. Sensitisation results in augmented and altered stimulus responses whereby light stimulation of the skin has as strong an effect as regular needling on the pain inhibitory system in FMS.

Central sensitisation in FMS is also associated with expanded receptive fields of central neurons resulting in a larger topographic distribution of the pain. This would suggest that control procedures using needling away from the 'specific site' might have as strong an effect as needling within the most painful area. Also, repeated nociceptive input from muscles (as obtained by *de qi*) results in expansion of receptive fields which in turn may result in activation of descending pain inhibition outside the stimulated myotome.

Sensitisation to pain, such as in FMS, may also be related to abnormalities in descending efferent pathways. As there is likely to be an imbalance between excitatory and inhibitory systems in FMS, stronger stimulation may therefore be needed to activate the descending pain inhibitory system. In studies using mild manual acupuncture or weak EA stimulation optimal pain inhibition may therefore not have been obtained.

When conducting studies on acupuncture, the clinical condition or syndrome needs to be taken into account and the control procedure designed accordingly.

Keywords

Acupuncture, fibromyalgia syndrome, pain, placebo, sensitisation, sham control.

Introduction

In recent reviews evaluating the efficacy of acupuncture in fibromyalgia syndrome (FMS) it has been concluded that acupuncture has no specific effects since the control procedure (superficial needling and/or needling away from the 'specific' points) has similar effects.[1-11] A prerequisite for these conclusions is that the control procedure used is inert and without specific effects. FMS is a chronic syndrome characterised by diffuse or specific muscle, joint, or bone pain, fatigue, and a wide range of other symptoms. The term fibromyalgia, coined in 1976 to more accurately describe the symptoms, originates from the Latin word *fibra*, meaning fibre, and the Greek words *myo*, meaning muscle, and *algos*, meaning pain. The defining symptoms of FMS are chronic, widespread pain and tenderness to light muscle touch and moderate to severe fatigue. Those affected may also experience heightened sensitivity of the skin. In patients with FMS non-noxious stimuli give rise to pain, allodynia, and noxious stimuli cause pain that lasts longer and has higher intensity than normally, hyperalgesia. FMS is also characterised by muscle ache, muscle spasms, weakness in the limbs, and 'nerve' pain.[12-22]

Pain in FMS

Central sensitisation of sensory neurons and pain disinhibition may explicate parts of the phenomenon seen in FMS.[13-19;23] Central sensitisation implies spontaneous nerve activity, expanded receptive fields of central neurons, resulting in a larger topographic distribution of the pain, and augmented stimulus responses such as abnormal temporal summation.[19;24-27] Peripheral sensitisation of sensory neurons innervating deeper tissues may also play a role.[25;28]

In FMS, sensitisation of sensory transmission neurons in the central nervous system (CNS), especially the wide-dynamic-range (WDR) neurons, becomes permanent. The WDR neurons change in structure, phenotype, function and biochemistry. Afferent Aδ nerve fibres that normally transmit sensations like touch, pressure and vibration get qualities that are similar to those of the thin afferent C-fibres (pain afferents). This implies that touch or slight pressure becomes painful.[24;25;27]

Abnormal temporal summation, or 'wind-up', is the phenomenon whereby after an initial painful stimulus, subsequent equal stimuli are perceived to be more intensely painful.[29] This magnified 'second pain', which occurs in everyone, is exaggerated in patients with FMS.[26] The receptor thought to be responsible for these phenomena is the N-methyl-D-aspartate (NMDA) receptor,[30;31] which is found at the postsynaptic membrane in the dorsal horn of the spinal cord. These receptors are normally inactive and do not respond to initial acute stimuli. However, after repeated neuronal depolarisation, the receptors undergo activation. Experimental evidences from animal and human studies have shown that NMDA receptors are responsible for wind-up and central sensitisation. NMDA receptors also play a critical role in neuronal plasticity and long term potentiation.[32;33] It is likely that the NMDA receptors contribute to the pain in FMS[24;25] as the temporal summation is attenuated by antagonists to NMDA receptors.[19;27;34-45] Interestingly, it has been reported that electroacupuncture modulates the expression of NMDA receptors in primary sensory neurons,[46] and regulates NMDA receptor NR1 subunit expression,[47] suggesting that part of the effects of acupuncture may be attributed to modulation of NMDA receptor activity.

Whether activation of glial cells is important for the pathogenesis of pain and allodynia in FMS is currently unknown.[48-50] Glial cells, long thought to be metabolically inactive support cells in the nervous system, are now recognised as playing a substantial role in modulating pain signalling.[48] Glial cells and astrocytes are activated by stimuli that induce pain, such as nerve trauma, subcutaneous irritation, and intraperitoneal inflammation,[49] and by neurotransmitters involved in pain signalling.[47] In addition to having receptors for neurotransmitters, glial cells express receptors for bacteria and viruses,[51-55] which may explain why infection with neurotropic organisms, such as HIV, is frequently associated with FMS or chronic pain. Glial cells release many neuroactive substances on activation by painful stimuli, including nitric oxide, prostaglandins, leukotrienes, nerve growth factors, excitatory amino acids, and reactive oxygens.[55] Activated glial cells induce the release of substance P and other excitatory amino acids from primary afferent neurons in the spinal cord and enhance the excitability of pain transmission neurons. In addition, microglia and astrocytes release proinflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor.[54] Increased levels of cytokines have been found in patients with FMS implicating a role in the aetiology of pain.[56-58] Blocking the actions of these cytokines prevents or reverses exaggerated pain states.[59] Also, acupuncture has been shown to inhibit glial activation and inflammatory events including hyperalgesia.[60;61]

Pain assessment and gender differences

To allow for assessment of the central sensitisation and the effects of acupuncture a reliable clinically applicable procedure is needed. We suggest that one such procedure is the assessment of matched pain and pain threshold using electrocutaneous stimulation,[62-65] though women's and men's assessment should preferably be evaluated separately.[66] This recommendation is based on findings from a recent study where gender differences in pain perception were assessed following acupuncture. This study aimed to investigate changes in electrical sensory thresholds and electrical pain thresholds, in response to electroacupuncture (EA) in healthy women and men.[67] The thresholds were assessed pre-, during-, and post-EA. Equal levels of

systematic changes (changes in common for the group) towards increased electrical sensory thresholds were seen in women and men post-EA. At the same point of time, systematic changes towards increased electrical pain thresholds were only seen in women, while they were unchanged in men. Significant individual variations were found in the women's responses of assessed electrical sensory and pain thresholds but not in the men's. It is concluded that both women and men responded with a significant increase of the electrical sensory threshold to EA, but only women responded with increase of the electrical pain thresholds though with individual variation.

A great individual variation in response to acupuncture suggests that it is not possible to make a prediction about expected effects for the group and that the treatment should be tailored individually. From an individual patient perspective the only true evaluation of a treatment is to try it out (presupposed a safe treatment with limited side-effects). This suggestion is valid even if randomised controlled trials (RCTs) have concluded that there are limited effects of a treatment, since this conclusion often is based on the results of the group, ignoring the individual effects. These and other findings indicate that in evaluation of acupuncture treatment gender differences should be taken into account as well as the individual variation.

Control and treatment parameters

Superficial needling versus deep needling

Patients with FMS suffer from allodynia, fatigue and muscle ache partly explained by peripheral and central sensitisation. Sensitisation results in augmented and altered stimulus responses whereby light stimulation of the skin might have as strong an effect as regular needling on the pain inhibitory system in FMS, despite being used as an 'inert control'. This suggestion is supported by studies measuring blood flow in patients with FMS where superficial needling of the skin resulted in as strong an increase in blood flow as stimulation of muscle tissue. In healthy subjects superficial needling had no effect on blood flow.[68;69]

Needling at specific points versus 'placebo' points

Recordings from neurons in the spinal dorsal horn have revealed that within minutes after application of a noxious stimulus to a receptive field in a muscle, new receptive fields at a distance from the initial receptive field emerge.[70-79] That is, following nociceptive input, dorsal horn neurons that were previously responsive to only one area in a muscle begin to respond to nociception from areas that previously had not provoked a response.[28;71] This may be attributed to activation of NMDA receptors on WDR neurons causing additional release of neuropeptides such as substance P, and these substances can diffuse in the spinal cord and result in the spread of pain.[20;37;42;57] Also, because of the several connections that exist between groups of glia and the types of transmitters they release, activation of glial cells may cause expansion of the receptive field or extraterritorial pain.[48;49] This central sensitisation could explain the large topographic distribution and the referred pain seen in FMS. This would suggest that control procedures using needling away from the 'specific site' might have as strong an effect as needling within the most painful area.

Also, repeated nociceptive input from muscles (as obtained by *de qi*) results in expansion of receptive fields, which in turn may result in activation of descending pain inhibition outside the stimulated myotome, ie if one uses, 'non-specific' ('placebo') points outside the affected myotome (most painful area/s) there may still be an effect.[80;81]

Altogether this would suggest that 'non-specific' points or sites do not exist in FMS. This may be true in other conditions as well.

Modality of stimulation

The endogenous pain modulation in FMS is impaired as compared to healthy controls.[82-85] This disinhibition of pain is a result of a change in the endogenous descending pain-modulating system. The descending system includes a nervous network that links the periaqueductal grey and the rostral ventromedial medulla with the spinal cord.[86] In persons with permanent pain hypersensitivity there could be a continuous stimulation of both facilitatory and inhibitory tracts that would result in increased pain if activity in inhibitory tracts decreases or if activity in facilitatory tracts increases.[87] The descending facilitatory pathways originate in the frontal cortical areas,[88] and have been shown to cause generalised increased neuronal responses

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along the neuroaxis, indicating that emotions such as fear may drive the development of widespread pain and sensitisation.[24-25]

As there probably is an imbalance between excitatory and inhibitory systems in FMS, stronger stimulation may therefore be needed to activate the descending pain inhibitory system. In studies using mild manual acupuncture or weak EA stimulation, optimal pain inhibition may therefore not have been obtained. This suggestion is supported by a study showing that strong electroacupuncture stimulation was needed to obtain pain alleviation in FMS.[89]

However, clinical experiences indicate that some FMS patients experience more pain when treated with acupuncture. This would indicate that depending on the status of the pain inhibitory system two responses may be obtained. When there is a light to moderate dysfunction of endogenous pain inhibition, strong stimulation may prove to be effective and when there is a severe dysfunction no pain inhibition is obtained and instead the treatment results in more pain. This would suggest that both 'light' and 'strong' stimulation should be tried out. The patient should then be allowed to continue with the stimulation modality preferred, thereby also optimising expectancy.[90-91]

Future perspective

In many randomised control trials a treatment is compared with its inactive control. However, a prerequisite is that one can design an appropriate control procedure. This may not be possible when assessing the effects of procedures like acupuncture. We therefore suggest that treatment procedures (for example 10 treatments by an acupuncturist versus a visit to a physician prescribing a drug which is then used) should be compared instead of separate treatments. Also, the efficacy of acupuncture should be compared with the recommended drug and its placebo taking side-effects, compliance and costs into account. In the future, environmental aspects of drugs (production, degradation etc) should be taken into account for the evaluation of optimal treatment strategies.[92-103]

Concluding remark

Taken together this would suggest that when conducting studies on acupuncture one needs to take the clinical condition or syndrome into account and design the control procedure appropriately.

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