STIMULATION-BASED ANALGESIA TECHNIQUES: DO THEY HAVE A ROLE TO PLAY IN POST-OPERATIVE PAIN MANAGEMENT?

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Abstract

Despite the advances in surgical procedures and analgesia options, post-operative pain (POP) remains a challenge. Modest efforts have been made to incorporate non-pharmacological, stimulation-based analgesia techniques in POP management with the hope of better control of pain and reduction of analgesic medication and side effects.

Pain is a complex phenomenon, involving both sensory-discriminatory and affective-cognitive processes. Many levels of the peripheral and central nervous system are involved in the transmission, modulation and integration of nociceptive information – the 'pain matrix'. Recent research has demonstrated that acupuncture and the-like stimulation-based techniques exert their effect via modulation of the 'pain matrix' both at the periphery and on spinal cord /brain level.

The majority of RCTs' and systematic reviews' results demonstrate acupuncture and TENS to be effective in reducing analgesic intake, side effects and pain intensity as part of standard POP management. The crucial factor for their effectiveness lies in the location, mode, intensity, timing and duration specifics of the stimulation they produce. Future research should concentrate on studying what the most effective and clinically applicable stimulation characteristics are.

Keywords: Post-operative pain, analgesia, acupuncture, TENS, stimulation-based techniques

Pain following surgery is an undesired, but extremely common occurrence. Although surgical techniques and procedures, as well as analgesia options have improved tremendously in the past few decades, 10-50% of patients are estimated to develop persistent chronic pain, which can be severe in 2-10% of cases (Kehlet et al, 2006). This increases the human (distress and suffering) and economic (higher morbidity and prolonged hospitalisation requirements) costs of surgery both in the short and long run. As the guiding principal of today's healthcare system is to provide clinically effective and cost efficient service, there is a strong impetus to optimise and standardise clinical interventions such as post-operative pain (POP) management (Rosenquist & Rosenberg, 2003).

Opioid and anti-inflammatory (paracetamol, steroid and NSAID) pharmacological preparations provide the main analgesia in POP management. Although their effectiveness and safety are continuously improving, there are still serious risks associated with their side effects. Opioids can cause respiratory and GI tract depression, nausea and vomiting, urinary retention and ileus, dizziness, lowered mental awareness and confusion. NSAIDs are associated with GI tract bleeds, renal damage and cardiac problems (Breivik, 1995; Spacek, 2006). These side effects are especially pronounced in the elderly, which are becoming an ever-larger group of elective surgery patients (Rakel & Herr, 2004; White, 2002).

Over the last 20-30 years, with the increase of knowledge of the physiology of pain, temptative efforts have been made to incorporate non-pharmacological analgesia techniques in order to minimise the use of opioids, reduce adverse events and speed-up recovery and hospital discharge (Rowbotham, 2005). The two main adjunct non-pharmacological modalities in POP management are stimulation-based analgesia and psychological intervention. This review focuses only on the most frequently used external (minimally invasive), peripheral stimulation-based analgesia techniques: acupuncture in its different modes of application - Manual Acupuncture (MAc), Electro-Acupuncture (EAc) and Auricular Acupuncture (AAc), as well as non-invasive acupuncture and nonacupuncture point stimulations - Transcutaneous Electrical Nerve Stimulation (TENS), Acupuncture-like Transcutaneous Electrical Nerve Stimulation (AlTENS) and acupressure. The criteria for choosing these techniques are based on availability of published articles rather than on assumed higher clinical effectiveness. This is not a comprehensive review – a limited number of recent articles were analysed with the objective to find out if there is sufficient justification for the incorporation of these analgesic techniques in the POP management protocols.

Post-operative pain

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey et al, 1979). This definition attempts to express the dual nature of pain: sensory-discriminatory and affective-cognitive. In reality the physiological nature of pain (nociception) is very complex, involving multiple interactions of neural networks from the periphery – to spinal cord – to brain and back to spinal cord and periphery – the so-called ‘pain matrix’ (Melzack & Wall, 1965).

Pain can be generally classified in few sub-types according to the mechanisms of the underlying pathology and neuro-pathophysiology: inflammatory pain, neuropathic pain, visceral, cancer and chronic non-specific pain (Falquhar-Smith, 2007). Pain generating events can occur at the periphery, involving somatic tissue, viscera or nerve tissue, as well as in the spinal cord or in higher supra-spinal regions of the CNS along the ‘pain matrix’ neuro-axis. Post-operative pain shares the same general characteristics (Spacek, 2006) with any other somatic pain. It is location and surgical procedure specific and it is different in nature at different stages in the post-operative period (Kahlet et a., 2006). In the immediate stages, the surgical incision and tissue manipulation produces actual tissue damage with ensuing inflammatory responses. Often during surgery nerve fibres get also severed or compressed, so the resulting pain has concomitant characteristics of both inflammatory and neuropathic pain. Taking into account the vulnerable and unstable physical, mental and emotional state of a patient after a surgical procedure (malaise, stress, anxiety and apprehension) and it is easy to see how the acute pain can lead to maladaptive plasticity and development of persistent chronic pain states (Kehlet et al, 2006). In order to avoid that, adequate post-operative analgesia is crucial. The following paragraphs attempt to summarise the main interactions between the different links in the 'pain matrix' and identify potential targets for stimulation-based analgesia techniques.

Inflammatory pain is a direct result of activation and excitation of primary nociceptive afferent (PNA) neurons by tissue damage (mechanical, thermal or chemical) in injury and surgery. A variety of different inflammatory substances get released in the interstitium by damaged cells, platelets, immune cells and the nerve endings themselves: prostaglandins, cytokines, histamine, bradykinin, serotonin (5-HT), norepinefrine, substance P (SP), Neurothrophic factors and many more (Farquhar-Smith, 2007). This continuous chemical excitation of the afferent neurons has a two-fold effect on nociception: firstly, it hyper-excites the primary nociceptive afferent (PNA) neurons with corresponding plastic changes (up and down regulation of gene-expression, ion channel and receptor activity and distribution), which lowers their resting potential and causes primary sensitisation and increased firing; secondly, the increased continuous bombardment of the second order neurons in the Dorsal Horn (DH) leads to their sensitisation (neural plasticity changes associated with NMDA, AMPA, GABA and opioid receptors and ion channels pre- and post-synaptically), which leads to increase of nociceptive signals being conducted to other parts of the Central Nervous System (CNS) – other spinal laminae and segments and higher brain centres. Inflammatory pain is associated with two phenomena – hyperalgesia and allodynia, which result from primary and secondary sensitisation. In the initial stages of tissue damage inflammatory pain directly corresponds in intensity to the underlying pathology, but if the local and descending inhibitory control is ineffective (there could be many reasons for inadequate higher centres pain suppression: psychological and emotional, physiological and metabolic, genetic) the sensation of pain can persists for longer than the actual tissue damage and lead to central sensitisation with plastic changes in the sub-cortical and cortical regions of the CNS (Woolf and Salter, 2000; Kehlet et al, 2006; Dickenson, 2007).

Pharmacologically, inflammatory pain is treated with paracetamol, NSAIDs and steroids, which form an important part of standard POP management. Traditionally acupuncture is commonly used to reduce pain and inflammation and there have been few studies confirming its anti-inflammatory action. Electro-acupuncture (EAc) has been shown to increase the plasma concentration of corticosterone in rats (Li et al, 2007), reduce peripheral SP concentration (Cao & Wang, 1989) and enhances the degranulation of mast cells (Zhang et al, 2007). Another interesting study (Wang et al, 2006) illustrated the reduction of hyperalgesia and primary sensitisation by EAc to be connected with down-regulation of expression of NMDA receptors in the central pre-synaptic terminals of small nociceptive fibres in the Dorsal Root ganglion (DRG). As inflammation is a common consequence of surgery, acupuncture and electro acupuncture demonstrate potential to counteract the overexcitement of the primary nociceptive afferents, reduce the primary sensitisation and contribute to the POP management in the initial stages after surgery.

Neuropathic pain is a direct result from damage to nerve tissue – in the periphery (as is the case of most surgical procedures) efferent and afferent axons get damaged. The ensuing neuroma (the proximal end of the damaged axon) begins to spontaneously fire – ectopic pacemaker-like activity, which leads to bombardment of DH neurons (Kehlet et al, 2006; Dickenson, 2007). The neuroma is also associated with abnormal sprouting and ion channels expressions and migration as well as recruitment in the Dorsal root ganglion (DRG) of neighbouring unaffected afferent fibres. All this leads to maladaptive plasticity in the DH and secondary sensitisation with symptoms of hyperalgesia, allodynia and concurrent hypoaesthesia (Kehlet et al, 2006).

Chronic (also known as clinical) pain is characterised by nociception in the absence of clear clinical pathology. Its nature is complex and not fully understood. It is accepted (Dickens, 2007) that there is maladaptive plasticity involving multiple links in the descending pain control system (both inhibitory and facilitory) from the mid-brain and brainstem as well as local spinal circuits. Ultimately, the aim of any analgesic treatment is to prevent the formation of chronic pain states.

Descending Inhibitory System (DIS), Diffuse Noxious Inhibitory Control (DNIC)

Many nuclei of the medulla, midbrain, thalamus and hypothalamus, limbic system, prefrontal and somato-sensory cortices are involved in the integration and modulation of nociceptive information (Apkarian et al, 2005; Peyron et al, 2000). The different circuits have specific roles to play – discrimination of the spatial, temporal and intensity specifics of the stimulus, affective and emotional response, memory, volition and coordination of motor and autonomic functions and so on. Their main output converges in the midbrain and brainstem – Periaqueductal Grey (PAG), Nucleus Raphae Magnus (NRM), Locus Coeruleus (LC) and Rostro Ventral Medulla (RVM) from where the major serotonergic, opiodergic and noradrenergic inhibitory pathways project directly to DH secondary and primary afferent nociceptive neurons as well as local spinal inhibitory interneurons (Purves, 2004; Farquhar-Smith, 2007). The DIS is the principal top-down regulation and modulation of pain mechanism in the nervous system. Majority of its inhibitory effect is produced by release of endogenous opioid neurotransmitters in the DH of the spine – β-endorphin, enkephalins and dynorphin, which inhibits both the primary afferents and prevents the firing of the secondary DH neurons. This is the pharmacological rational for the use of opioid analgesics to prevent the sensation of pain.

Activation of the DIS and release of endogenous opioids is one of the principal mechanisms of action of stimulation-based analgesia – widely accepted as the mode of action of traditional manual acupuncture (MAc) and electro acupuncture (EAc) (Han et al, 1999; Han, 2003; Han, 2004). There are numerous papers published in the last 10 years of brain imaging (fMRI and PET) studies on brain activation during acupuncture points stimulation (Dhond et al, 2007a; Dhond et al, 2007b; Napadow et al, 2005; Napadow et al, 2007; Dougherty et al, 2008; Hsieh et al, 2001), which confirm that. They share many common findings, which demonstrate areas of activation and deactivation in the 'pain matrix', consistent with the understanding of the function of DIS.

Another possible mode of activation of the DIS and endogenous opioid release is the Diffuse Noxious Inhibitory Control (DNIC) phenomenon. Le Bars and colleagues (1979) reported suppression of the activity of nociceptive Trigeminal neurons in the medullary DH after conditioning painful stimulation anywhere on the body, irrespective to the area or tissue type. Bing and colleagues (1991) demonstrated that acupuncture produces similar action to DNIC. Their results show that manual acupuncture stimulation at Zu San Li (S36) acupoint on the lower limb of a rat produced very similar pain conditioning inhibition of the Tigeminal convergent neurons as emerging the hindpaw in hot water.

Spinal 'Gating' (SG)

In the sixties Ronald Melzack and Patrick David Wall (1965) postulated an exciting new theory of integration and modulation of nociceptive signals in the DH – the spinal 'gate'. They reasoned that there must be substantial interaction in the DH between PNA (C fibers), non-nociceptive afferents (A β fibers), local inhibitory interneurons and secondary projection neurons. In summary, when thick myelinated fast conducting A β fibers get stimulated, they can over-ride the excitation in the DH produced by signals from the nociceptive slow conducting C fibers and suppress the firing of the secondary projection neurons – close the 'gate'. Although quite simple, this theory has helped to explain some of the mechanisms of action of stimulation-based techniques such as acupuncture and TENS. Not everybody agrees with the specifics of type of fibers involved. Kawakita and Okada (2006) point out that acupuncture points' location is based on traditional theory, which postulates that acupoints can simultaneously be stimulated by needling (mechanical) and burning moxa (thermal). As A β fibers are not associated with transmission of heat signals, they put forward that other A-type fibers (Aδ) connected with polymodal receptors should be considered the main afferents conducting acupuncture and the-like stimulations.

As illustrated in the previous paragraphs, substantial research into the mechanisms of pain as well as analgesia and the mechanisms of action of acupuncture and similar type of stimulation-based techniques has been done all over the world. Although complete understanding is far from been achieved, there are clear indications of the analgesic potential of stimulation-based techniques. The following paragraphs review the data coming from clinical trials of different types of acupuncture and TENS, used for the treatment of post-operative pain (POP).

Acupuncture and related techniques

Acupuncture is an age-old therapeutic technique, used for millennia in East Asia for the treatment of disease and promotion of health. It is based on the traditional anatomo-physiological understanding of the inter-connectedness between the different parts of the human body via the acupuncture meridian system. The principal role of the meridians is to control homeostasis and coordinate the metabolism of all the tissues in the body by distributing Qi (a vital substance closely connected with the blood, which has its origin in the nutrients and water of the food and air, as well as other regulatory substances produced by the body itself) (Cheng, 1987). Although anatomically there is no such a structure that resembles the classical acupuncture meridians, recent research (Langevin and Yandow, 2002) has found a strong connection between location of acupuncture points and organisation of the extracellular connective tissue matrix. From modern anatomo-physiological perspective, acupuncture meridians are better viewed as functional rather than anatomical entities, which closely overlap with the function of the nervous, endocrine and immunological systems - the overarching neuro-endocrine-immune system (Claw and Chrousos, 1997).

Nowadays acupuncture is practiced extensively all over the world by classically trained acupuncturists (Chinese, Japanese, Korean and other traditions), as well as western-trained doctors, physiotherapist and other health professional. There is considerable variety in both theoretical underpinning and practical application of acupuncture to such a degree, that sometimes the only common ground between different style acupuncturists is the use of solid needles, rather than points and stimulation type specifics. This is well illustrated in the latest definition of acupuncture by the Department of Health sponsored Acupuncture Regulatory Working Group in the UK. In their report (2003) they defined acupuncture as ''...the insertion of a solid needle into any part of the human body for disease prevention, therapy or maintenance of health. There are various other techniques often used with acupuncture, which may or may not be invasive''.

This lack of unity and consensus on what constitutes a clinically effective treatment makes acupuncture very difficult to study in an experimental design setting. The blinded, placebo controlled clinical trial, which has become the gold standard, further complicates the situation. No wonder there are many inconsistent and, sometimes, conflicting results in randomised clinical trials (RCT) of acupuncture. This is also reflected in the RCTs of the use of acupuncture for POP management.

In a recent systematic review of acupuncture and related techniques for POP, Sun and colleagues (2008) identified 126 studies, but due to inadequate quality (not RCT, lack of placebo, no post-operative measurements) only 15 met the inclusion criteria. The included RCTs varied to the type of surgery (abdominal gynaecological, thoracic, knee and hip, and oral/molar), to the mode of acupuncture point stimulation (MAc, EAc, AAc, acupressure and capsicum plaster acupoint application), as well as to time of initiation and length of treatment (pre-, post- and throughout the whole peri-operative period). Their main outcomes were post-operative opioid consumption and pain intensity for the first 8, 24 and 72 hours, recovery room stay and opioid-related side effects: nausea, sedation, pruritis and urinary retention. The results of their meta-analysis showed that the acupuncture treatment reduced significantly opioid consumption in the first 8, 24 and 72 hours respectively by 21%, 23% and 29%. The pain intensity also was reduced, but reached significance only at 72 hours. Unsurprisingly the opioid-related side effects were lower in the acupuncture group. Sun and colleagues concluded that acupuncture and related techniques are effective opioid-sparing adjuncts to conventional POP management, as suggested by the evidence. As limitations to their study, they pointed out the variability of acupuncture regiments, stimulation types, placebo/sham controls, timing of intervention, outcome measures and small size of trials, which in their view, leave many questions unanswered.

My search has identified only one recent RCT (Michalek-Sauberer et al, 2007), which has failed to show effectiveness of acupuncture for POP and analgesia consumption in third molar tooth extraction surgery. In this study Michalek-Sauberer and colleagues investigated electrical stimulation and auricular acupuncture peri-operatively from 30 minutes before the operation to 48 hours post-operatively. Their protocol involved three different types of Auricular points stimulation: group one had embedded ear needles plus electric stimulation (EA); group two had only embedded needles plus sham electric stimulation (AA) and group three (the control) had small metal plates attached with sham electric stimulation (NN). The three different groups varied demographically only marginally – the EA had significantly more smokers and female patients. The pain intensity, analgesic consumption (Acetaminophen) and rescue medicine requirements (Mefenamic acid) did not differ significantly between the groups. Their conclusion was that neither electrical auricular acupuncture, nor auricular acupuncture alone, was effective for reducing pain intensity and analgesic consumption for molar tooth extraction POP.

Two other independent studies (Lao et al, 1995; Tavares et al, 2007) also evaluated the effectiveness of acupuncture on POP in identical type of molar extraction oral surgery. In contrast to Michalek-Sauberer and colleagues' study, both of them found acupuncture to be effective in reducing pain intensity and analgesic requirements. The acupuncture protocols employed in their studies were, however, quite different from the previous study. Lao and colleagues used MAc on classical acupoints on the legs and face post-operatively against a sham treatment (non-penetrating taped needles) immediately after the operation and again when the pain increased. Tavares and colleagues, on the other hand, combined both 5 classical body acupoints (upper and lower extremities and face) as well as 2 auricular points, which were stimulated both manually and electrically 24 hours prior to the operation and immediately after the operation. The patients themselves were used as a control in this study – one molar extraction was performed with and the other without acupuncture in a random order in different patients.

There are few possible explanations for Michalek-Sauberer and colleagues' results. As there was no 'no-treatment' group in their study it is difficult to confirm that stimulation of the three auricular points was ineffective. As the points on the ear are very superficial (directly under a thin layer of skin against the ear cartilage), auricular acupuncturists often tape seeds to patient's ears, relying on the direct mechanical stimulation for the therapeutic effect. Michalek-Sauberer and colleagues' control group had small metal plates taped to the auricular points, so it is possible that this was not an ''inactive'' treatment. The electric stimulation device was worn for over two days by the participants, which almost half of them found uncomfortable and irritating. This could have interfered with the relaxing and analgesic effects of the treatment and distorted the results. It is also possible, that the choice of acupuncture points and/or auricular acupuncture in general are not the most effective method for relieving acute POP oral pain as it is in other acute POP conditions (Usichenko et al, 2005).

These are just few examples, which illustrate the importance of the specifics of the acupuncture and related techniques in respect to point selection, type of manipulation, timing and duration. All these techniques produce their therapeutic effect by feeding information (signalling) in the system - for example electrical stimulation at different frequencies leads to different opiods release: 2Hz – endorphins and 100 Hz – dynorphin (Han, 2003). It is only logical to assume that the system would respond differently to stimulation with different special, temporal, frequency and intensity characteristics.

Transcutaneous Electrical Nerve Stimulation (TENS)

RCTs in the effectiveness of TENSE for POP management, further illustrate the challenges of stimulation-based therapeutic techniques research. As with the acupuncture techniques, the crucial factor for the effectiveness of TENS application lies in the specifics of the stimulation it produces.

TENS is passing low voltage electrical pulses via surface adhesive electrodes, which has been extensively used in physiotherapy for pain control (Kotze and Simpson, 2007). The electrodes are usually attached close to the area of pain, on the same segmental dermatome. When the electrodes are placed over an acupoint, TENS is referred to as ALTENS. TENS is thought to exert is analgesic effect via stimulation of predominantly Aβ fibers and controlling the ‘spinal gate’ and release of endogenous opioids (Kotze and Simpson, 2007).

In the late nineties, a team at the University of Texas conducted studies (Chen et al, 1998; Hamza et al, 1999; Wang et al, 1997), which investigated how the specifics (location of electrodes placement, frequency and intensity) of the TENS stimulation reflected its effectiveness for POP after abdominal (hysterectomy) surgery. Their results demonstrated TENS to be effective in reducing opioid requirements and related side effects, when used as part of the POP management protocol. They also found that the location of electrodes placement next to the incision is as effective as when placed over Zu San Li (S36) acupoints on the lower legs and significantly more effective (37% and 39% opioid intake reduction) compared to sham TENS and inappropriate location (shoulder) TENS (Chen et al, 1998). Hamza and colleagues' study (1999) demonstrated that different frequencies (2Hz, 100Hz and mixed 2/100Hz) TENS produce different outcomes. All the TENS stimulations reduced significantly the need for analgesics, but the mixed 2/100Hz stimulation had grater effect (53% versus 32% and 35% in the 2Hz and 100Hz respective reduction compared to sham treatment). Wang and colleagues (1997) examined the effect of the intensity of TENS stimulation. The results of their RCT demonstrated that high (subnoxious) intensity TENS is significantly more effective in reducing opiod requirements (65%) compared to no treatment - low intensity TENS group achieved 34% and sham TENS 23% reduction.

In light of the findings of the studies in the previous paragraph, not taking the specifics of the TENS stimulation into account could very easily lead to conflicting results in RCTs. Unsurprisingly, two systematic reviews of TENS in POP management have reached totally opposite conclusions. Carroll and colleagues (1996) in their meta-analysis emphasised predominantly the importance of randomisation in TENS studies of POP, but failed to take into account, that only few of the studies included in their analysis had used stimulation with sufficient intensity. Consequently they concluded that TENS does not provide any benefit for POP in respect to pain intensity and analgesic consumption. Bjordal and colleagues' systematic review (2002), on the other hand, reached totally opposite conclusions – TENS, when administered with adequate intensity and appropriate frequency could significantly reduce analgesic consumption for POP. These discrepancies further confirm that, when investigating effectiveness of stimulation-based techniques, the specifics of the produced stimulation are of paramount importance.

Conclusions

The progress made in the past few decades in the field of neuro-biology and neuro-pharmacology has lead to great improvements in pain management and treatment. The tremendous increase in knowledge of the intimate molecular, cellular and systemic mechanisms involved in pain processing have also opened the door for the investigation of age-old stimulation-based techniques like acupuncture. Although we are far from understanding all the mechanisms of action of acupuncture (and the-like techniques), research evidence clearly demonstrates the major effect acupuncture stimulation produces on peripheral (PNA), spinal cord (DH) and supra-spinal level of the central nervous system.

In the area of POP management, evidence from RCTs and systematic reviews points out that both acupuncture and TENS are useful adjunct to standard POP management, reducing the analgesic requirements, side effects and pain intensity. The crucial factor in their ability to produce significant clinical effect is appropriate and adequate stimulation in respect to location, mode, intensity, timing and duration.

The majority of modern research has focused on pharmacological interventions of molecular and cellular signaling. That has led to the development of new, more effective drugs, but there have always been limitations to the success of transferring new theoretical knowledge into clinically effective drug treatments. The main obstacle often originates from the systemic way pharmacological agents are administered in practice (oral, intravenous, intramuscular and subcutaneous injections and so on). Although they target specific cell receptors, they affect many more cells than intended, producing undesired side effects, which limits their clinic applications.

Recent research, especially in acupuncture, has demonstrated that stimulation-based techniques produce their effect also through signaling. The difference is that the signaling produced is direct and specific to the characteristics (location, mode, intensity, timing and duration) of the stimulation, which modulates the many controlling functions of the nervous system. Future research of stimulation-based techniques should concentrate on studying what the most effective and clinically applicable stimulation characteristics are, both for pain and other clinical conditions.

References

Apkarian VA, Bushnell CM, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J of Pain 2005; 9:463-484.

Bing Z, Villanueva L, Le Bars D, Acupuncture-evoked responses of subnucleus reticularis dorsalis neurons in the rat medulla. Neuroscience 1991; 44:693–703.

Bjordala JM, Johnsonb MI, Ljunggreen AE, Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. European Journal of Pain 2003; 7:181–188.

Carroll D, Tramer M, McQuay H, Nye B, Moore A. Randomization is important in studies with pain outcomes: systematic review of transcutaneous electrical nerve stimulation in acute postoperative pain. Br J Anaesth 1996; 77(6):798–803.

Chen L, Tang J, White PF. The effect of location of transcutaneous electrical nerve stimulation on postoperative opioid analgesic requirement: acupoint versus nonacupoint stimulation. Anesth Analg 1998; 87:1129–34.

Cheng X (Chief Ed.). Chinese Acupuncture and Moxibustion. Foreign Languages Press. Beijing 100037, China.

Clauw DJ & Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997; 4:134–153.

Dhond RP, Kettner N, Napadow V, Neuroimaging Acupuncture Effects in the Human Brain. The Journal of Alter. and Compl. Medicine 2007a; 13(6):603–616.

Dhond RP, Kettner N, Napadow V, Do the neural correlates of acupuncture and placebo effects differ? Pain 2007b; 128(1–2):8–12.

Dickenson A. The neurobiology of chronic pain states. Anaesth and Intensive Care Med 2007; 9(1):8-12.

Dougherty DD, Konga J, Webba M, Bonabc AA, Fischmanc AJ, Golluba RL, A combined [11C]diprenorphine PET study and fMRI study of acupuncture analgesia. Behavioural Brain Research 2008; 193:63–68.

Ernst E, Lee H, Pittler MH, Shin BC, Lee MS. Acupuncture for the treatment of post-operative pain. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD006042. DOI: 10.1002/14651858.CD006042.

Farquhar-Smith PW, Anatomy, physiology and pharmacology of pain. Anaesthesia and Intensive Care Medicine 2007; 9(1):3-7.

Hamza MA, White PF, Ahmed HE, Ghoname EA. Effect of the frequency of transcutaneous electrical nerve stimulation on the postoperative opioid analgesic requirement and recovery profile. Anesthesiology 1999; 91(5):1232–8.

Han JS, Acupuncture and endorphins. Neuroscience Letters 2004; 361:258–261.

Han JS, Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies. TRENDS in Neurosciences 2003; 26(1):17-22.

Han Z, Jiang YH, Wan Y, Wang Y, Chang JK, Han JS, Endomorphin-1 mediates 2 Hz but not 100 Hz electroacupuncture analgesia in the rat. Neurosci. Lett. 1999; 274:75–78.

Hsieh JC, Tua CH, Chenc FP, Chena MC, Yeha TC, Chenga HC, Wua YT, Liuc RS, Ho LT, Activation of the hypothalamus characterizes the acupuncture stimulation at the analgesic point in human: a positron emission tomography study. Neuroscience Letters 2001; 307:105-108.

Kawakita K & Okada K, Mechanisms of action of acupuncture for chronic pain relief – polymodal receptors are the key candidates. Acupuncture in Medicine 2006; 24:58-66.

Kehlet H, Jensen TS, Woolf CJ, Persistent postsurgical pain: risk factors and prevention. Lancet 2006; 367:1618–25.

Kotzé A, Simpson KH, Stimulation-produced analgesia: acupuncture, TENS and related techniques. Anaesthesia and Intensive Care Medicine 2007; 9(1):29-32.

Langevin HM & Yandow JA. Relationship of acupuncture points and meridians to connective tissue planes. The Anatomical Record (New Anat) 2002; 269:257–265.

Lao L, Bergman S, Langenberg P, Wong RH, Berman B. Efficacy of Chinese acupuncture on postoperative oral surgery pain. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995; 79:423–8.

Li A, Zhang RX, Wang Y, Zhang H, Ren K, Berman BN, Tan M, Lao L, Corticosterone mediates electroacupuncture-produced anti-edema in a rat model of inflammation. BMC Comp. and alter. Medicine 2007; 7; 27; doi:10.1186/1472-6882-7-27.

Melzack R & Wall PD, Pain mechanisms: A new theory. Science 1965; 150: 171-9.

Merskey H, Allbe-Fessard D, Bonica JJ, Carmon A, Dubner R, Kerr FWL, Pain terms: a list with definitions and notes on usage. Recommended by the IASP subcommittee on taxonomy. Pain 1979; 6:249–52.

Michalek-Sauberer A, Heinzl H, Sator-Katzenschlager SM, Monov G, Knolle E, Kress HG. Perioperative Auricular Electroacupuncture Has No Effect on Pain and Analgesic

Consumption After Third Molar Tooth Extraction. Anesth Analg 2007; 104:542–7.

Napadow V, Webb JM, Pearson N, Hammerschlag R. Neurobiological correlates of acupuncture: November 17–18, 2005.J Altern Complement Med 2006;12:931–935.

Napadow V, Kettner N, Liu J, et al. Hypothalamus and amygdala response to acupuncture stimuli in carpal tunnel syndrome. Pain 2007; 130:254–266.

Peyron P, Laurent B, Garcia-Larrea L. Function imaging of brain responses to pain. Areview and meta-analysis. Neurobiophysiol Clin 2000; 30:263-288.

Rakel B & Herr K, Assessment and Treatment of Postoperative Pain in Older Adults. Journal of PeriAnesthesia Nursing, 2004; 19(3):194-208.

Rowbotham DJ, Recent advances in the non-pharmacological management of postoperative nausea and vomiting. British Journal of Anaesthesia 2005; 95(1):77–81.

Spacek A, Modern concepts of acute and chronic pain management. Biomedicine & Pharmacotherapy 2006; 60:329–335.

Sun Y, Gan TJ, Dubose JW, Habib AS, Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. British Journal of Anaesthesia 2008; 1-10; doi:10.1093/bja/aen146.

The Acupuncture Regulatory Working Group. The Statutory Regulation of the Acupuncture Profession, the Report of the Acupuncture Regulatory Working Group. Published By The Prince of Wales's Foundation for Integrated Health, 2003. www.fihealth.org.uk

Usichenko TI, Dinse M, Hermsen M, Witstruck T, Pavlovic D, Lehmann C. Auricular acupuncture for pain relief after total hip arthroplasty—a randomized controlled study. Pain 2005; 114:320–7.

Wang B, Tang J, White PF, Naruse R, Sloninsky A, Kariger R, Gold J, Wender RH. Effect of the intensity of transcutaneous acupoint electrical stimulation on the postoperative analgesic requirement. Anesth Analg 1997; 85(2):406–13.

Wang LN, Zhang Y, Dai J, Yang JP, Gang SC, Electroacupuncture (EA) modulates the expression of NMDA receptors in primary sensory neurons in relation to hyperalgesia in rats. Brain Res. 2006; 1120:46–53.

White PF, The Role of Non-Opioid Analgesic Techniques in the Management of Pain After Ambulatory Surgery. Anesth Analg 2002; 94:577–85.

Woolf CJ and Salter MW, Neuronal plasticity: increasing the gain in pain. Science 2000; 288:1765–9.

Zhang D, Ding GH, Shen XY, Yao W, Zhang ZY, Zhang YQ, Lin JY, Influence of mast cell function on the analgesic effect of acupuncture of ‘‘Zusanli’’ (ST 36) in rats. Acupunct. Res. 2007; 31:147–152 (in Chinese, English abstract).