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Oxytocin - A Possible Mediator of Anti Stress Effects Induced by Acupuncture?

Oxytocin, a polypeptide containing nine amino acids, is produced in the paraventricular and the supraoptical nuclei of the hypothalamus. Oxytocin is secreted into the circulation to produce hormonal effects such as stimulation of milk ejection and uterine contractions. In addition, oxytocin is released from oxytocin containing nerve fibres that reach various areas in the brain, such as other parts of the hypothalamus, the amygdala, the raphe nuclei, the PAG, the striatum and the brainstem centres for control of autonomic function. Thus oxytocin may influence endocrine functions, but also exert anxiolytic and sedative effects, elevate pain threshold, decrease sympathetic nerve activity and increase vagal parasympathetic nerve activity. Taken together oxytocin induces a psycho-physiological pattern consistent with increased social behaviour, anti-stress and promotion of growth. These effects become particularly prominent if oxytocin is given repeatedly. Five daily injections of oxytocin elevate pain threshold for 10 days after the last injection and blood pressure may be reduced for up to three weeks in female rats. When the anti-stress is established it can be maintained by treatment given at longer intervals.

The long-term effects of oxytocin and some of the acute effects are mediated by secondary changes in the activity in other transmitter systems. The pain relieving effects involve an increased activity in central opioid systems e.g. in the PAG, whereas the anti-stress effects are mediated by an enhanced activity in the α_2 adrenoceptors in various brain areas reached by oxytocin containing nerves. Since these receptors exert an inhibitory effect on noradrenaline (NA) release, the activity in the central NA bundles emanating from the locus coeruleus, which is linked to arousal and aggression, is decreased. At the same time activation of EPI neurons in the brainstem lead to an inhibition of the peripheral sympathetic system, and an increase in the activity of the parasympathetic system, and as a consequence anti-stress and growth promotion is induced.

Originally it was assumed that oxytocin was only released during labour and breastfeeding in response to activation of sensory nerves in the mammary gland and uterus. However, it has recently been established that oxytocin can be released in response to touch, warmth and light pressure from all parts of the body. Obviously stimulation of non-noxious somatosensory afferents does not only result in 'a localised sensation of touch', it also results in physical relaxation and a sense of well-being. In a rat model, in which the abdomen is being stroked with a frequency of 40 strokes per minute for 5 minutes, all the effects that can be induced by oxytocin (increased friendly social interaction and the anti-stress effects) are induced. Administration of an oxytocin antagonist inhibits the effects of the massage-like stroking acutely, but also the long-term effects seen after repeated treatments. Interestingly, the massage-like stroking induces more powerful effects if applied on the ventral surface. This can be an effect that is secondary to the denser innervation of this region. However, immunohistological studies have revealed the presence of an extra type of sensory nerve originating in the skin on the ventral surface. These do not project to the spinal cord, but directly to the vagal nerve to reach the NTS. Thus some of the cutaneous afferents travel to the brain via the afferents from the viscera e.g. the gastrointestinal tract. The NTS is in turn directly connected to the PVN where oxytocin is produced. It is possible that activation of these special cutaneous afferents lie behind the more powerful effects of touch, warmth and light pressure,

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when triggered from the ventral surface.

The mechanisms by which acupuncture induces its effects are only partly known and are under debate. However, particularly the long-term anti-stress effects of this treatment may well include activation of oxytocinergic pathways and mechanisms. Some animal experimental data indicate that pain relief induced by acupuncture is abolished not only by opioid antagonists but also by oxytocin antagonists. Oxytocin has also been shown to alleviate back and cancer induced pain in humans. Further studies are needed to explore the relationship between oxytocin and the effects of acupuncture.

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Acupuncture Mechanisms and the Relevance to Clinical Practice

Acupuncture is part of traditional Chinese medicine, a system with an empirical basis that has been used in the treatment of pain for centuries. Its use for pain relief is supported by clinical trials and this has facilitated its acceptance in pain clinics in most countries. Acupuncture effects on pain must devolve from physiological and/or psychological mechanisms with biological foundations. Acupuncture and some other forms of sensory stimulation elicit similar effects in man and other mammals, suggesting that they bring about fundamental physiological changes. Acupuncture excites receptors or nerve fibres in the stimulated tissue which are also physiologically activated by strong muscle contractions and the effects on certain organ functions are similar to those obtained by protracted exercise. Both exercise and acupuncture produce rhythmic discharges in nerve fibres, and cause the release of endogenous neurotransmitters including opioids, monoamines, oxytocin and other neuropeptides (SP, CGRP, GAL, CRF, NPY), important in the control of both sensory, affective and cognitive elements of pain.

Over the past ten years there has been a growing awareness that pain is due not simply to the activation of peripheral nociceptors, as in nociceptive pain, but to multiple factors, and is therefore susceptible to various modes of acupuncture treatments. Depending on the aetiology, pain may be classified into several categories, such as nociceptive, neurogenic, chronic pain syndrome and psychogenic pain.

Musculoskeletal and visceral pain states, both nociceptive, are characterised by hyperalgesia. However, despite belonging to a similar category, the pain is triggered by different mechanisms. Neurogenic pain is caused by injury or dysfunction in the nervous system and is often severe and intractable and may not respond to even powerful opioids. Recent studies suggest that there is a third pain category, distinct from the neurogenic and nociceptive, where pain is related to a sickness response that occurs with exposure to chemical compounds and infectious agents the associated central changes produce heightened pain sensitivity ('hurting all over'), termed chronic pain syndrome. In clinical trials acupuncture or low frequency electroacupuncture have shown to be effective in some nociceptive pain states, whereas high frequency stimulation is more effective in neurogenic pain. In chronic pain syndrome patients with high anxiety, acupuncture is generally inefficient. It is possible that part of the lack of effect in chronic pain syndromes can be attributed to high levels of the opioid-antagonist cholecystokinin in the brain.

Acupuncture may be effective in some categories of pain but the mode of stimulation should be adjusted to the aetiology of pain. Also, patients are likely to respond better if they are not stressed and anxious.

Acupuncture for Infertility in Women

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Introduction

This summary is intended to illustrate *Acupuncture for Infertility in Women*, as an example of a method of treatment that has become more established in western medicine over the last decade. Discussed are the scientific documentation, the physiological basis for the use of acupuncture and evidence for the use of acupuncture in this area. There are unfortunately few well-designed papers on the effectiveness of acupuncture in the field of infertility. The underlying mechanisms of acupuncture are often described in the language of traditional Chinese medicine (TCM), and surprisingly few penetrating discussions have dealt with the physiological background of acupuncture.

Working Hypothesis

What is it that makes us think that acupuncture can have an effect on different conditions in reproductive medicine? In acupuncture both physiological and psychological mechanisms may be involved.¹ Much simplified it could be explained as follows. Both acupuncture and electroacupuncture (EA) stimuli excite mechanoreceptors with low and high thresholds in muscles and other tissues. By stimulation of muscle afferents in somatic segments according to the innervation of the ovaries and the uterus, it is thought that inhibitory systems in the spinal cord are activated, resulting in segmental inhibition of sympathetic outflow and pain pathways as predicted by the gate control theory. At the same time, interneurons connected to higher control systems are excited. This results in the release of β -endorphin via two different systems.

One system includes the hypothalamus and neuronal network that projects to the midbrain and brainstem nuclei which in turn activate two pain-alleviating, descending neuronal pathways: the serotonergic (5-HT) and the noradrenergic (NA) systems. There is also evidence that the hypothalamic β -endorphin system has a central role in changes seen in autonomic functions after acupuncture. This is probably due to an inhibition of the vasomotor centre (VMC) resulting in a sustained decrease of general sympathetic tone.

In the other system β -endorphin is released into the blood stream from the hypothalamus via the anterior pituitary. This release is regulated by corticotropin-releasing factor (CRF). CRF promotes the release of β -endorphin, adrenocorticotrophic hormone (ACTH) and melanocyte-stimulating hormone (MSH) in equimolar amounts through stimulation of the synthesis of their precursor pro-opiomelanocortin (POMC). These hormones exert their effects in different target organs via the bloodstream. Stress increases the activity of the hypothalamo-pituitary-adrenal (HPA) axis and decreases reproductive functions.

In addition, acupuncture is probably one of the most effective non-pharmacological methods in terms of activating placebo effects. Indeed, acupuncture works by stimulating endogenous opioids and so, it appears, does the placebo effect.

The described findings with regard to the central β -endorphinergic release and the decreased sympathetic tone support the idea that EA may be effective in reproductive medicine.

Is there evidence for the use of acupuncture for infertility in women?

Many childless couples hoping for pregnancy try acupuncture, but what evidence do we have today that tell us if acupuncture affects the pregnancy rate? There are a large number of studies when a suitable search is performed on Medline – most of them are in Chinese or Russian, and have only abstracts in English. Below is a review of some relevant articles in the area.

Gerhard et al (1992):² Infertility – Auricular Acupuncture

Of ninety infertile women with recognised hormonal disorders, 45 received auricular acupuncture over 12 sessions and 45 matched controls received conventional hormonal therapy. Pregnancy rates were no

different between the groups. Side-effects were fewer, and tendency to miscarry was lower, in the acupuncture group.

Xiaoming et al (1993):³ Undefined Anovulation

Thirty-four women with undefined ovulatory dysfunction were treated on average 30 times with manual acupuncture according to TCM theory. Twelve got biphasic basal body temperature curves (BBT) in more than two cycles and/or became pregnant. In addition, a regulatory effect on plasma concentrations of gonadotrophins and oestrogen, indicates an influence on the HPG axis.

Chen et al (1991):⁴ Anovulation – Polycystic Ovary Syndrome (PCOS)

Eleven women with anovulation (nine with PCOS) and five healthy controls were given 4-5Hz EA for ovulation induction, three days per cycle in three cycles. Ovulation induction was shown in 6 of 13 cycles, in the anovulatory women. The plasma β -endorphin concentrations decreased and the hand skin temperature increased significantly after EA treatment. The EA effect was attributed to an inhibition of high activity in the sympathetic nervous system.

Stener-Victorin et al (2000):⁵ EA – Anovulation – PCOS

Twenty-four women with PCOS (typical ultrasonographic appearance, no more than four episodes of bleeding per year) were given 2Hz EA twice a week for two weeks and then once a week, altogether 10-14 treatments. Interestingly, the LH/FSH ratio, the testosterone concentrations and the β -endorphin concentrations decreased significantly following EA when all the participants were analysed together and blood samples before the EA period were compared with the samples taken three months after the last EA treatment. This result is also supported by experimental data.^{6,7}

In conclusion, it appears that acupuncture may have a beneficial effect on women with PCOS and anovulation, and might serve as a complement to first line therapy in ovulation induction supported by both clinical and experimental evidence. Acupuncture has not been shown to improve the pregnancy rate, and there is a need for more RCTs in well-defined populations.

Applications in human assisted reproduction

Endometrial circulation

Successful IVF and ET requires optimal endometrial receptivity at the time for implantation. The endometrial circulation, or, blood flow impedance in the uterine arteries, measured as the pulsatility index (PI), is considered valuable in assessing endometrial receptivity. A PI value above 3.0 will result in no pregnancy.

Stener-Victorin et al (1996):⁸ EA and Uterine Artery Blood Flow Impedance

Ten women with a PI value above 3.0 were given 2/100Hz EA twice a week for four weeks – altogether eight treatments. PI measurements with transvaginal ultrasound were made before down regulation, before the first EA treatment, and directly after the last treatment (that is the eighth). The mean PI was significantly reduced, both directly after, and 10-14 days after, the eighth EA treatment.

In conclusion, EA improves the blood flow impedance, but we don't know if this correlates with an increased implantation rate – further studies with larger numbers of patients in each group will be needed to determine the latter.

Oocyte aspiration

Oocyte aspiration is performed using a transvaginal approach, with puncturing of the vaginal wall to reach the follicles. It's the most painful component in the IVF procedure, and a successful outcome often requires 2 to 3 trials. That EA induces adequate analgesia during a minor operation is not a new observation and can be referred to a clinical area where trials already exist.

Stener-Victorin et al 1999.⁹ EA compared with Alfentanil as Anaesthesia during Oocyte Aspiration

The effect of EA (2/100Hz) in combination with a paracervical block (PCB) as anaesthesia during oocyte aspiration was compared with a fast acting opioid (alfentanil) in combination with PCB.

In conclusion, EA in combination with PCB has, in two trials, been shown to be as good as alfentanil and PBC for induction of sufficient intra-operative anaesthesia during oocyte aspiration. The women have less postoperative pain, seem to recover faster. In addition, women in the EA group received significantly less additional alfentanil. Such a reduction is most likely preferable because alfentanil has been found in the follicular fluid shortly after IV injection. We were not able to show that EA improves the pregnancy rate.

General conclusion

It must be pointed out that unless substantiated by research, the therapeutic use and acceptance of acupuncture cannot be extended with confidence. In any case, the arguments against alternative treatments in the recently published debate article of Renckens,¹⁰ are not relevant and have minimal, if any, scientific basis. It is, of course, unethical to promise cure and recovery when the method used lacks evidence of an effect. On the other hand, it is also unethical to disallow a method that demonstrably works. There are few well-designed papers on the effectiveness of methods of treatment that are not generally established in western medicine, but the field is not best summarised as ‘much ado about nothing’. We need to stick to basics and have open scientific minds.¹¹

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Acupuncture in the Treatment of Addiction

Acupuncture has been used in the treatment of addiction in the West since an incidental observation in Hong Kong in 1973.¹ Opium smokers who had been given electroacupuncture for pain relief claimed that their opioid withdrawal symptoms were less severe than they expected. Subsequently, various forms of needle or electrical stimulation have been used as a treatment for dependence on various addictive drugs, with the specific aim of reducing withdrawal symptoms and aiding cessation. Auricular acupuncture is now used in about 500 centres in the USA for chemical dependency, mainly cocaine and heroin addiction.

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Smoking cessation

Uncontrolled studies have suggested that acupuncture might reduce the symptoms of nicotine withdrawal and some remarkably high rates of initial success have been claimed. For example, one study claimed that 95% of 194 subjects were not smoking after three treatments in one week, falling to 34% after twelve months.² A large study of 514 subjects claimed 88% success. However, only randomised sham-controlled studies can determine whether this is more than a placebo effect. The Cochrane Review has recently been updated which aims to determine the effectiveness of acupuncture and the allied therapies of acupressure, laser therapy and electrostimulation in smoking cessation.³

Methods

We searched the Cochrane Tobacco Addiction Group trials register, Cochrane Controlled Trials Register, Medline, Embase, BIOSIS Previews, PsycINFO, Science and Social Sciences Citation Index, AMED and CISCOCOM. Randomised trials comparing any of these forms of stimulation with either sham treatment, another intervention or no intervention for smoking cessation were selected for the review. We assessed abstinence from smoking at the earliest time-point (before 6 weeks) in order to identify an early effect on withdrawal symptoms. We also assessed outcomes at six months and at one year or more follow-up. We used sustained abstinence figures, when available, and biochemically validated rates. Those lost to follow-up were counted as continuing to smoke. Data for smoking cessation rates were extracted from the reports by the first two authors independently. Where appropriate, we performed meta-analysis using a fixed effects model.

Quality of studies

The quality of the 22 identified studies was assessed in various ways. A study was adjudged to be single-blind if it involved some form of sham therapy that was designed to be indistinguishable to the participant, even if the word 'blind' was not specifically mentioned by the author. There were 14 such studies of acupuncture. Achieving full double-blinding is problematic in acupuncture studies. One trial achieved blinding of the therapist by training a novice to use the two interventions without knowing which was genuine. Both subjects and therapists were blinded in one study that used subthreshold electrostimulation. Another study was labelled 'double-blind' by the authors because subjects and assessors, though not therapists, were blinded.

Even if subjects are blinded, they may be influenced by the interaction with the practitioner. To avoid this, minimal or standardised interaction between therapist and patient is a recognised method of reducing bias in acupuncture research. This procedure was mentioned in 4 reports of studies. Smoking cessation was verified by biochemical testing in seven of the trials using either a carbon monoxide meter, or serum or urinary cotinine concentrations. Only 6 of the studies measured outcomes at 12 months.

Results

Acupuncture was significantly superior to waiting list in the early results (OR 5.88, 95% CI 2.66 to 13.01), but there was no difference at 6 months (OR 0.99, 95% CI 0.30 to 3.24). The one study with results at 12 months gave an OR of 2.44 (95% CI 1.15 to 5.20). Acupuncture was not superior to sham acupuncture in smoking cessation at any time point. The odds ratio (OR) for early outcomes was 1.22 (95% confidence interval 0.99 to 1.49); the OR after 6 months was 1.50 (95% confidence interval 0.99 to 2.27) and after 12 months 1.08 (95% confidence interval 0.77 to 1.52). Similarly, when acupuncture was compared with other anti-smoking interventions, there were no differences in outcome at any time point. The results with different acupuncture techniques do not show any one particular method (i.e. auricular acupuncture or non-auricular acupuncture) to be superior to control intervention.

Based on the results of single studies, acupressure was found to be superior to advice; laser therapy and electrostimulation were not superior to sham forms of these therapies.

Conclusions

There is no clear evidence that acupuncture, acupressure, laser therapy or electrostimulation are superior to placebo for smoking cessation. This should be interpreted in the context of the major impact that smoking cessation is known to have on health. The results of two recent high quality trials suggest that sustained stimulation may be a crucial factor for success,^{4,5} and future studies using this form of intervention are justified.

Cocaine dependence

The Yale team, headed by Drs Avants and Margolin, have produced the most rigorous research to date on the place of acupuncture in treating cocaine dependence. The form of acupuncture used is the NADA protocol. After careful pilot studies to establish the most appropriate form of acupuncture control procedure, they conducted two RCTs of acupuncture compared with sham acupuncture and with relaxation procedure. In the first study with 82 patients, acupuncture was significantly better than either relaxation or needle insertion control.⁶ In the second, multi-centre study involving 620 patients, there were no differences between the groups in either cocaine use or treatment retention over 8 weeks.⁷ The disagreement in the results may have been at least partly due to differences in the methods of the studies.

Alcohol dependence

Alcohol dependence has been the subject of rather few controlled trials of acupuncture. An early influential study among 80 recidivist alcoholics found that those who had real acupuncture were much more likely to stay in treatment.⁸ However, a replication of the study in 56 alcoholics failed to support those findings.⁹ A third study concluded that electroacupuncture (whether at appropriate or inappropriate sites) in addition to standard treatment was better at reducing cravings than standard treatment alone.¹⁰

In summary, acupuncture appears to be better than no intervention for the treatment of addiction, but the present evidence does not suggest that it is superior to sham that involves needling.

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Acupuncture in Stroke Rehabilitation

Acupuncture and electroacupuncture stimulate skin and muscle afferents. Intracellular recordings of cortical neurons in primates as well as neuroimaging and neurophysiological studies in humans have shown that cortical sensorimotor representation areas can be modified by sensory stimulation. Experimental studies have demonstrated that acupuncture has circulatory and biochemical effects in common with physical exercise on the release of transmitters and peptides in the brain and spinal cord.¹

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Acupuncture has been used for the treatment of stroke patients in China from ancient times and is increasingly applied in stroke patients in western countries. Beneficial results have been reported in studies with different designs and treatments starting from 24 hours to 8 years after stroke onset. Although not generally accepted in the absence of convincing evidence of efficacy, the panel of the NIH Consensus Development Conference on Acupuncture stated in 1998 that: "There are other situations such as ...stroke rehabilitation ...where acupuncture may be useful as an adjunct treatment of an acceptable alternative or be included in a comprehensive management program".² Few studies have been randomised and the use of control or sham groups have varied. An earlier study from my own department indicated a strikingly positive and lasting effect.^{3,4} However, although it was a randomised study, the effect of acupuncture was compared to controls with no alternative treatment.

The conclusion from a later randomised controlled multicentre trial was that there was no evidence for any specific effect of acupuncture.⁵ Three treatments were compared: acupuncture including electroacupuncture, low frequency high intensity transcutaneous nerve stimulation (TNS) and subliminal high frequency low intensity TNS. It should be pointed out that even a subliminal stimulus (not perceived by the patient) may have an effect on the brain; furthermore, the simple fact of placing an electrode on the skin can lead to some brain activation. Thus the information to the patients was that all of them received one of three types of sensory stimulation.

The most likely explanation to the difference between the two studies is that the positive effect in our earlier study was due to expectation. We know that our thinking and our expectations have effects on the brain. Although it used to be believed that placebo effects are always transient, that might not be true and there is no theoretical reason why effects achieved by expectation could not be lasting.

Another point could be that during the time between the two studies a better general organisation of stroke care had positive effects that increased the outcome in all the three groups. Possible support for this interpretation is that the ADL improvement in all three groups was closer to the former acupuncture than to the former control group. However, another randomised study including a group with no sensory stimulation also failed to show any superiority of acupuncture.⁶

Current data on brain plasticity indicate that various types of sensory stimulation, training and activation can influence rehabilitation. Housing animals in an enriched environment after brain lesions interacts with various therapeutic interventions including drug treatment and transplantation. From experimental as well as clinical data methods combining sensory stimulation of various types and physical activity are likely to be most efficient.

Questions that have not been answered by our studies are whether acupuncture, low frequency TNS or other types are of value in specific subgroups of stroke patients. Studies with more homogenous patient populations combined with better evaluation methods may be more fruitful than multicentre studies to find such subgroups. There are some unavoidable problems with multicentre studies that will be discussed. However, to be able to generalise recommendations regarding acupuncture we need to show that the method works at more than one centre.

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Future Directions for Acupuncture Research

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Excitation following nociceptor activation or paroxysmal activity in afferent nerves triggers sets of neuronal events which extend over a time frame ranging from milliseconds to hours, days or weeks. In addition to traditional treatments, new regimes to prevent or trigger activity-dependent long-term changes in transducing and suppressive systems for pain are emerging.

In recent years traditional pain treatments such as acupuncture became accessible to the analytical power of modern electrophysiological, molecular and cellular biological techniques. These recent advances in pain research underline the importance of multireceptive neurones in the establishment of hyperalgesia and allodynia, which are under the control of inhibitory interneurons on various stages in the neuraxis. The first stage of sensory integration in the dorsal horn of the spinal cord reflects the earliest short-term responses such as neuronal discharge activity as well as the long-term changes that most commonly require alterations in gene expression. In general, activity-dependent gene expression and the transient modulation of synaptic transmission by, for example, phosphorylation of ion channels, greatly expands the capacity of highly integrated systems, such as the pain matrix, to react in a more plastic manner to environmental stimuli. Acupuncture stimuli may interact with neuronal circuits on various levels of the neuraxis. It is feasible to assume that this treatment evokes neuroplastic changes and alters gene expression in various components of the pain matrix, for example, in cortical and subcortical areas integrating pain threshold and intensity. Enhanced neuronal excitability is the therapeutic target of acupuncture. Imaging techniques can now be used to relate peripheral stimulation of traditional and non-traditional acupuncture points and pain perception. Animal experiments suggest that numerous neurons in pain related structures lower their excitability under such a treatment. An enhancement of the discharge rate of such tonically active inhibitory interneurons would finally lower the activity in neurons involved in pain processing. Under physiological conditions their activity probably prevents acute pain signals from triggering long-lasting excitability increases in projection neurons.

Acupuncture in Anaesthesia

Introduction

Despite the long history of acupuncture, the first surgery under acupuncture analgesia without additional anaesthetics was reported as being performed in 1958 in China. This impressive introduction of acupuncture into anaesthesia was part of the political concept of Mao Tse Tung to combine traditional Chinese medical techniques and modern western medical concepts. The enthusiastic reports from China inspired acupuncturists and anaesthetists in the seventies, mainly from Austria and Germany to introduce acupuncture analgesia for surgery and to develop combined anaesthetic techniques. But these techniques remained experimental and were never used widely in routine practice.

In Europe and America acupuncture became popular in the treatment of chronic pain conditions. Nevertheless according to a NIH consensus conference on acupuncture in 1997 the best evidence of the efficacy of acupuncture is shown in two other, more anaesthesia relevant conditions. According to the literature it was stated that promising results showed efficacy of acupuncture in adult postoperative and chemotherapy nausea and vomiting and postoperative dental pain (NIH 1998).¹

The purpose of this review is to show the history and potential of acupuncture in anaesthesia from the view of western medical journals.

Acupuncture Analgesia in Anaesthesia

The first report of acupuncture analgesia for surgery in a western medical journal can be found in 1971 in *JAMA*.² One year later in 1972 the first surgery in acupuncture analgesia in Europe was reported from Vienna, Austria, when a tonsillectomy was successful performed without any other anaesthetics.³ These

procedures needed intensive preoperative preparation of the patient, usually additional premedication and sometimes application of local anaesthetic or intravenous analgesics during surgery. Later, especially in Europe, acupuncture analgesia was combined with general anaesthesia to improve patient comfort. Induction was usually performed with barbiturate and muscle relaxants, and controlled ventilation was maintained with oxygen and nitrous oxide. With this combination rapid recovery, cardiovascular stability and reduction in the need for opioid drugs, was reported in heart surgery,⁴ as well as in thyroid surgery, abdominal surgery and eye surgery. All together more than 700 cases of acupuncture analgesia were reported in 1976 in the German journal *Anaesthetist* (volume 25).

Later some controlled studies were performed. In the *Lancet* in 1978 acupuncture analgesia was reported to be more effective than sham acupuncture for gastroscopy.⁵ In a study using acupuncture analgesia for abdominal surgery,⁶ 90% less fentanyl was necessary than without acupuncture. In oocyte aspiration for IVF, acupuncture compared favourably to alfentanil in terms of pain and nausea, although patients in the acupuncture group experienced more stress and discomfort than those in the alfentanil group.⁷

Only a few studies were performed to investigate the effect of acupuncture on volatile anaesthetic consumption. In a recent investigation TENS of an auricular acupuncture point was able to decrease volatile anaesthetic requirement of desflurane in volunteers.⁸

Depending on the author, or the location of the surgery, a variety of acupuncture points were described for acupuncture analgesia. Distal points like LI4, PC6 and ST36 are used as well as segmental points, para-incisional points or ear points. The needles were stimulated manually or electrically (1-200Hz, 1-40mA). Usually stimulation of the acupuncture points started about 20 minutes before surgery and was continued during the operation.

In most of the reports disadvantages of acupuncture analgesia were discussed. These include the technique being time consuming, lack of complete analgesia, the possibility of being a non-responder, discomfort and awareness.

Postoperative Pain Management

According to a review by Ernst and Pittler (1998), results of studies about acupuncture for postoperative dental pain were very promising.⁹ Results of studies about other postoperative pain conditions were contradictory. The reduction of postoperative pethidine with electroacupuncture after abdominal surgery in a controlled pilot study could not be repeated in a larger study by the same investigators.^{10:11} In knee arthroscopy acupuncture could not reduce postoperative pain.¹² In contrast recent studies showed decrease of postoperative opioid consumption by TENS or intradermal needles.^{13:14}

Postoperative Nausea and Vomiting (PONV)

Most randomised controlled trials (RCT) of acupuncture for the prevention of PONV exist for stimulation of PC6. In a review of 33 antiemesis trials, 21 were about PONV.¹⁵ A meta-analysis in 1999 found 19 RCTs with different stimulation at PC6, such as acupressure, manual acupuncture, electroacupuncture and TENS, with an overall good result concerning early nausea and vomiting, apart from PONV in children.¹⁶ But recent studies have shown significant effects for children in prevention of PONV with Korean hand acupressure,¹⁷ or intraoperative acupuncture and postoperative electrical stimulation at PC6.¹⁸

Discussion

This selection of western medical literature since 1970 shows a great interest in acupuncture amongst anaesthetists. Many reports described the challenging and successful attempts to perform acupuncture analgesia for surgery. Because of the practical disadvantages, the uncertainty of failure, and better modern anaesthetics, this method was never established. Subsequently studies have focused on the effect of acupuncture in managing postoperative pain. Some promising results need to be confirmed by further

RCTs.

The best evidence is given for prevention of PONV with acupuncture. However, the optimal timing of the intervention and the duration and intensity of the stimulus have yet to be clarified. Even the location of stimulation may be variable. Nevertheless, with further studies, there is a good chance that acupuncture may be used routinely to prevent PONV in the future.

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Neuroimmunomodulation – A Scientific Foundation for an Ancient Skill

The immune system represents a multisystem comprised of components derived from central nervous (CNS), endocrine (ES) and immune system (IS).¹ A term neuroimmunomodulation (NIM) was coined to describe the permanent intercommunication between these systems. They exchange information on the basis of shared receptors and biochemical substances.² By modulation of their production it is possible to affect the function of the immune system. The immunointervention could be achieved by direct influence on the immune system or indirectly by modulating activity of the CNS or Endocrine System (ES).

Evidence has been accumulated in recent years on the underlying pathophysiological mechanism of the acupuncture.³ Stimulation of different acupoints could produce a certain amount of neurotransmitters, neuromodulators, neurohormones and cytokines.⁴ They can either directly affect the components of the

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immune system or indirectly by activating the neuroendocrine axis. The main neuroimmunomodulators released after acupuncture stimulation are opioid peptides: the enkephalins, endorphins and dynorphins.^{5,6} The experimental results suggest a bi-modal, dose dependent effect of the opioid peptides on the immune system, met-enkephalin (Met-Enk) and leu-enkephalin (Leu-Enk) being the most extensively studied opioid peptides.⁷

It is now clear that Met-Enk and Leu-Enk are not equipotent since the former has been more active in modulating the immune response. Met-Enk injected peripherally in high doses suppresses, whereas in low doses enhances, immune reactions. Injection of Met-Enk into the cerebral cavity (ICV) of the rat sensitised with bovine albumin could modulate cutaneous delayed hypersensitivity to the antigen more effectively than when injected peripherally. So, delayed cutaneous reactions were increased after small dose intraventricular injection of Met-Enk, whereas the large dose of the same enkephalin induced decreased skin reactions.^{8,9}

At a certain dose Met-Enk could be a potent anti-inflammatory agent, or may even prevent anaphylactic shock.¹⁰

Enkephalins are able to prolong survival time of mice inoculated with tumour cells. In vivo treatment of cancer patients could also result in immunomodulation. Of great interest are the results that showed, *in vitro* as well as *in vivo*, that the enkephalins can enhance NK and T cell activity. Therefore by increasing activity of NK cells it would be possible to enhance host resistance to viral and tumour challenge.¹¹

The rapidly expanding area of NIM has become an unlimited source of data that has enabled us to understand and scientifically explain the ancient skill of acupuncture.

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Congress Proceedings

Abstracts from the highest scoring scientific free papers at the 10th International Congress of Medical Acupuncture and Related Techniques (ICMART) held in Edinburgh from 4th to 6th May 2002

One of the papers presented at the congress is published in full in this journal on pages 56-65.

Longer-Term Clinical and Economic Benefits of Offering Acupuncture to Patients with Chronic Low Back Pain Assessed as Suitable for Primary Care Management – 3 Month Clinical Outcomes from a Controlled Trial of 241 Patients.

Objectives

To undertake a pragmatic randomised controlled trial to test the hypothesis that a population of patients with persistent low back pain, when given access to an acupuncture service, gain more relief from pain than those offered usual management only, for equal or less cost.

Methods

The study is a pragmatic randomised controlled trial (n=241). Suitable patients are identified by their general practitioners. Patients randomised to the experimental arm are offered the option of referral for up to 10 individualised treatments from one of six qualified acupuncture practitioners. The control group continues to receive usual management from their general practitioner. The primary scale used for measuring change is the Bodily Pain (SF-36) at 3 months and 12 months post randomisation. The main outcome is cost-effectiveness at 12 months.

Results

A total of 43 general practitioners participated in the trial and 241 patients were randomised. All patients randomised to the option of acupuncture chose to receive treatment. Clinical outcomes at 3 months show that the SF-36 Bodily Pain scores improved by 29.4 and 24.9 points in the acupuncture and normal management group respectively (p=0.125). Patients in the acupuncture group reported lower levels of worry at three months (p<0.001).

Conclusions

It is possible to conduct a large pragmatic randomised controlled trial of acupuncture in a primary care setting. Acupuncture is seen as an acceptable treatment by patients with low back pain. Clinical outcomes at three months suggest that the acupuncture group are in less pain than the control group.

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Effects of Intensity of Electroacupuncture Stimulation Upon Mechanical Pain Thresholds in Healthy Human Volunteers: A Pilot Study

The issue of parameters of stimulation for optimal analgesic acupuncture effects has been debated extensively. Exploration of both experimental and clinical studies fails, however, to suggest appropriate parameter combinations for the optimal analgesic effects of acupuncture. The aim of the current pilot study was to explore the effects of intensity of stimulation (high versus low) upon experimentally induced mechanical pain (Mechanical Pain Thresholds – MPT) in healthy human volunteers.

Following ethical approval, 48 healthy, acupuncture-naïve, volunteers (24M, 24F) were recruited from the staff and student population of Keele University. After screening for relevant contraindications, subjects were allocated in randomised blocks (blocked by gender) to one of four groups: control, placebo, high-intensity, and low-intensity. Subjects in the control group had sham acupuncture needles

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(Streitberger & Kleinhenz, 1999) placed on four acupuncture points; these were attached to the electrostimulator, but no current was passed through the electrodes. Prior to this, a full demonstration and explanation of the workings of the sham needle were given. For subjects in the placebo group, four placebo needles (as above) were placed on the chosen acupuncture points and connected to the electrostimulator; subjects were told that they would be receiving electroacupuncture, but with currents of subliminal intensity. Subjects in the high-intensity and low-intensity groups received true needling on all four points and the needles were connected to the electrostimulator. Subjects in the high-intensity group were asked to report the level of stimulation when it became 'very strong, almost uncomfortable'. Subjects in the low-intensity group were asked to report the level of stimulation when it was 'quite strong, but in no way uncomfortable'. All treatment groups received stimulation (4Hz, 200msec) for 30 minutes and were observed for a further 30 minutes. MPT were taken at the first interosseous space of the dominant and non-dominant hands. These measurements were taken at baseline and at 10-minute intervals thereafter for the duration of the experiment – a total of seven measurements.

Results were analysed using repeated measures ANOVA, with gender as the blocking factor and baseline MPT as a covariate; alpha was set at 0.05. Differences were found in MPT between the groups in respect of both dominant hand ($F=3.361$; $p=0.028$) and non-dominant hand ($F=2.847$; $p=0.050$). Pairwise comparisons, with Bonferroni correction to maintain alpha at 0.05, revealed that MPT was significantly greater for the high-intensity group than for the placebo group for both the dominant hand ($p=0.021$) and the non-dominant hand ($p=0.036$). Other pairwise differences were non-significant. Cautious interpretation of these findings suggests that high intensity stimulation evokes not only segmental but also generalized hypoalgesia. Further studies with appropriate statistical power are now in progress to explore these findings in more detail.

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Does Acupuncture Contribute to the Treatment of Chronic Shoulder Pain (CSP) *[this paper was submitted but not presented]*

Objective

Response of Chinese acupuncture compared to conservative orthopaedic treatment and unspecific needling in pain treatment on CSP.

Design

Prospective, randomized controlled trial with three blinded parallel groups; follow up three months.

Setting

Outpatients of 26 orthopaedists, who have attended a 140 hours training course on acupuncture.

Patients

Four hundred and twenty seven out-patients with a history of CSP \geq six weeks, VAS \geq 50 mm were selected; three random groups, six weeks treatment. 308 patients reported after three months follow up. Two strata: age 25-45 and age 46-65.

Interventions

Group 1: VAP: 15 treatments of verum acupuncture (VAP). Group 2: SHM: 15 treatments of non-specific needling, sham acupuncture (SHM). Group 3: COT: conventional conservative orthopaedic treatment (COT). Patients were blinded to allocation between verum and sham acupuncture.

Main Outcome Measures

Primary endpoint: pain reduction \geq 50% on VAS three months after the end of the treatment protocol. Secondary endpoints: global assessments on a 4-score scale directly after the end of the treatment protocol.

Results

The results after three months follow up are: Highly significant effect of CAP over SHM and COT in the whole sample ($P<0.0001$) and in Stratum1 ($P<0.001$) and Stratum2 ($P<0.001$).

Conclusions

Acupuncture is an important supplement in the management of CSP.

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Validating a New Sham (Placebo) Acupuncture Device: Two Randomized Controlled Trials

Background

For clinical trials of acupuncture, it would be desirable to have a sham procedure that is indistinguishable from the real treatment, yet inactive. A sham needle has been designed which telescopes instead of penetrating the skin. The Park Sham Device involves an improved method of supporting the sham needle and requires validation.

Objective

To test whether the sham procedure using the new device is: 1. Indistinguishable from real needles, and 2. Inactive.

Design

Two subject and assessor-blind, randomized controlled trials. Study samples: Study 1: 58 patients included in a clinical trial of acupuncture for acute stroke. Study 2: 63 healthy, acupuncture naïve, adult volunteers.

Intervention: Real or sham acupuncture using the Park Sham Device. Settings: 1. District general hospital, 2. University laboratory. Measurements: 1. The form of treatment that patients believed they had received 2. Experience of de-qi, as judged by three acupuncture experts.

Results

Study 1: No patient in either group believed s/he had been treated with the sham needle. Study 2: In 40 volunteers for whom experts achieved consensus, the relative risk of experiencing de-qi with real acupuncture to that with sham acupuncture was 15.38 (95% CI 2.26 to 104.86). The inter-rater reliability of all 13 experts, calculated from their judgements on 10 subjects selected by randomisation, was 0.52 (95% CI 0.19 to 0.61).

Conclusions

Results suggest that the procedure using the new Park Sham Device is both indistinguishable from real acupuncture and inactive. It is therefore a valid control for acupuncture trials. The findings also lend support to the existence of de-qi, a major concept underlying traditional Chinese acupuncture.

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Neurogenic Pruritus: Treatment by Acupuncture

Introduction

Notalgia paraesthetica is a condition associated with itching, and unassociated with a rash, that affects a segment of the body innervated by T2-T6 dorsal spinal nerves. It is believed to be a type of neuropathy. This single-handed practice reports one such case. It also describes a further eight cases of "neurogenic" pruritus which share similar characteristics to this condition but are in segments of the body innervated by cervical and lumbar spinal nerves. Traditional acupuncture has been described to help with skin conditions and this study was performed to see if it was successful in this type of pruritus.

Patients and Methods

Over a nine-year period in a practice with an average list size of 2000 patients, nine patients aged 41 to 79 years presenting with segmental itching were identified. Other causes of pruritus were excluded by

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clinical examination, as well as by haematological and biochemical tests. Drug induced causes were also excluded. Duration of pruritus was six weeks (range 4 – 52 weeks). In eight patients itching was restricted to dermatomes innervated by the spinal nerves of the cervical spine, in two by the dorsal spine and in two by the lumbar spine. In three patients pruritus occurred in dermatomes innervated by two separate areas of the spine. Clinical examination revealed restricted cervical or lumbar movements in seven patients. Paravertebral tenderness and/or spasm of the paravertebral muscles was found in the areas of pruritus in seven patients. Skin changes associated with sympathetic nerve over-activity were noted in five patients. Six of the nine patients had x-ray evidence of degeneration of the spine.

Results

All nine patients were treated by deep intramuscular stimulation of the paravertebral muscles in the dermatomes affected by pruritus.

In total a median of three treatments (range 2 – 5) was required to resolve the pruritus. Recurrence of symptoms occurred in four patients within 8 to 12 months of their last treatment over a period of follow-up of 0.5 – 9 years (median one year). Repeat acupuncture treatment resolved the pruritus.

Discussion

The term neurogenic pruritus describes and encompasses all conditions associated with segmental itching unassociated with a rash. The clinical signs of this condition are suggestive of an early neuropathy as a result of a degenerative condition of the spine. This is the first report of symptoms of such a condition being treated successfully by acupuncture.

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Laser Acupuncture in the Management of Depression

Introduction

Traditional Chinese medicine (TCM) has long recognised the use of acupuncture in psychological medicine. Classically the acupuncture meridians or channels are each linked to particular emotions, for example, joy and sadness (heart channel), panic and anxiety (kidney channel), anger and frustration (liver channel). By correct diagnosis, acupuncture intervention can be useful in the restoration of emotional well-being. Today it is realised that this restoration of emotional health is due to neuromodulation at the higher centres. Results of the NIH funded depression study by Allen, Hitt and Schnyer (1998) were encouraging. The study demonstrated acupoint specificity ($p < 0.05$) for mood disorders. Unfortunately, the study was single blinded. This study is based on the NIH study. The research team hoped to reproduce the significant results achieved then. With laser as the modality, the advantages were obvious: non-invasive modality, randomised double blind control achievable, no infection risk and ease of training community-based doctors to utilise the technique.

Method

This pilot study utilised laser acupuncture in an outpatient population with mild to moderately severe depression with Beck Depression Inventory (BDI) scale of 12 to 30.

Normal was less than or equal to BDI of 10. Recruitment was through family practices (called general practices in Australia) and newspapers. Recruits were each screened by a psychiatrist to confirm their suitability. They were then randomised into sham laser and true laser groups. Each patient received twice a week sessions for a month, followed by once a week sessions for another month. BDI scores were taken fortnightly to ensure none of the patients deteriorated. The acupuncturist was also blinded. BDIs were repeated at one month and three months post laser.

Results

Thirty patients were recruited and randomised into true and sham laser. Four patients were withdrawn, two from each arm of the study. The rest completed the laser sessions. Of those who completed the study, one patient did not respond to any of the post laser follow up BDI requests. Another patient did not

complete the three-month follow up BDI. Results showed a markedly significant improvement in the active group ($p < 0.001$) at the end of the course of treatment with a sustained difference one month after treatment ($p < 0.05$).

Discussion

The markedly significant results were unexpected. They do however make laser acupuncture a serious contender as a third standard management option in the treatment of depression in the community. Laser acupuncture could stand alone, or be used together with counselling, psychotherapy or drug therapy. These latter areas of mixed management need to be explored. In the National Institute of Mental Health Treatment of Depression Collaborative Research Programme over 30% of participants terminated treatment early due to adverse effects, lack of improvement or desire to change therapies. These were based on psychological and/or pharmacological treatments. Patients were obviously searching for more satisfactory treatments, non-chemical in nature and without adverse effects. An important point to note from this laser study is that the series of treatments maintained their significance for the month after completion. This suggested that follow-up or maintenance laser acupuncture sessions were important for patient well-being and the one month mark could be indicative of appropriate timing.

The research team recommends larger and more specific studies to confirm these findings and explore the wider clinical implications. The team is keen to perform a multicentre study but is restricted by funding issues.

High-Frequency Electroacupuncture Suppresses Repeated Nicotine-Induced Behavioral Activation and C-Fos Expression in the Nucleus Accumbens of the Rats.

We have previously shown that repeated injections of nicotine produced an increase in locomotor activity, dopamine (DA) release and c-fos expression in the brain. Acupuncture as a therapeutic intervention is widely used for the treatment of many mental disorders and drugs of addiction including nicotine. In order to investigate whether acupuncture has an influence on nicotine-induced reinforcing and behavioural effects, the present study investigated the effect of electroacupuncture on nicotine-induced behavioural sensitisation and the expression of c-fos in the nucleus accumbens using Fos-like immunohistochemistry (FLI). The rats were given repeated nicotine injections (0.4 mg/kg, s.c., twice daily for seven days) followed by one challenge injection on the 11th day. Nicotine challenge produced a larger increase in locomotor activity and accumbal FLI in nicotine-pretreated rats. However, pre-treatment with high-frequency electroacupuncture at zusanli (ST36) and sanyinjiao (SP6), significantly attenuated an increase in nicotine-induced locomotor activity and accumbal FLI to subsequent challenge. These results demonstrated that 100Hz electroacupuncture inhibited nicotine-induced behavioral sensitization and c-Fos expression in the nucleus accumbens. The inhibitory effect of electroacupuncture on locomotor activity may reflect an inactivation of the mesolimbic DA system through the activation of the dynorphin, as evidenced by decreased FLI cells in the nucleus accumbens.

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