Summaries and commentaries by Adrian White on a selection of recent acupuncture studies

Clinical studies of effectiveness

Embryo implantation


A sham-controlled RCT of acupuncture on the day of embryo transfer, n= 635.

Methods

A total of 635 patients undergoing IVF or intracytoplasmic sperm injection (ICSI) were included. Embryo transfer was accompanied by either acupuncture or sham acupuncture. The acupuncture group were treated at GV20, ST29, PC6, SP8 and LR3 before embryo transfer, and GV20, LI4, SP6, SP10, and ST36 afterwards, all bilaterally except GV20. Depth of needling and method of stimulation were not described. The control group were given the Streitberger needle at the same points. Both interventions were applied for 30 minutes, before and after the embryo transfer. Conventional management of implantation followed one of two well known protocols.

Results

The groups had no differences at baseline and received the same conventional management. There was no significant difference between the groups for ongoing pregnancy rates which were 27% and 32% in acupuncture and control groups respectively, and corresponding live birth rates were 25% and 30%.

Comment

This study is large and appears ‘negative’ – though it would be over-simplistic to interpret it as meaning that acupuncture ‘cannot’ have any effect in embryo transfer. The overall implantation rate of about 50% is already reasonable and similar to that of all women in the hospital, so maybe there were ceiling effects that prevented any further increase. The acupuncture techniques were not fully described (depth, stimulation and sensation are missing), so the amount of stimulation might actually not have differed very much from that given via the Streitberger needle to the control group. Acupuncture was sometimes given by nurses trained specially for the trial. And finally, the choice of points is discussed below.

Of course, that is not the same as saying that study is false negative. The authors rightly recommend that the meta-analysis of all studies of acupuncture against sham should be updated to include their own plus that of So and colleagues in 2009.1 The result of this update is shown in Figure 1, and the odds ratio for clinical pregnancy is 0.86 [0.70, 1.05]. The two largest studies show that acupuncture needle penetration seems to have a negative effect on pregnancy.

Since infertility is an area where women continue to spend much time and money on acupuncture, it seems important to sort this out. The missing link in all this research is justification for the acupuncture protocol.

Anyone planning a clinical trial has to justify the way the intervention is applied with some kind of evidence, ideally evidence of the likely physiological mechanisms. But all these acupuncture studies justified their acupuncture regime only by stating that someone else had used it first! This is no justification at all. So none of the studies has done a proper test of an authoritative acupuncture treatment protocol.

The suggested mechanisms for any effect on embryo implantation generally involve the concept of increasing blood flow to the uterus. So studies should plan the best treatment protocol to achieve it. For example, Stener-Victorin has provided evidence for the efficacy of low frequency electroacupuncture in uterine blood flow.3 Studies should also select patients who have impaired blood flow where there is scope for improvement.

Many modern studies, including this one, are carefully designed for good internal validity and so appear to score highly for ‘quality’. But they are not designed as a fair test of acupuncture, and so are wasteful of resources and a disservice to patients and their health care system. They raise the question whether RCTs that do not justify their treatment protocol are even ethical.

REFERENCES


Labour pain


RCT of electroacupuncture for labour pain relief (n=350).
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Methods
Women in three centres with regular contractions and 2-3 cm cervical dilatation were randomised into electroacupuncture (EA), sham electroacupuncture and control groups. The EA group received the to 40 mm needles inserted 25-30 mm on the point SP6, with square wave electroacupuncture at 4Hz for 30 minutes. The sham group had mock needle insertion (but could not see the site) and an EA machine was placed within their vision. The control group had usual care.

The analgesic effect was self-rated by women in labour, using visual analogue scale (VAS). Progress of delivery, safety and outcome were assessed by the duration and paralysis time of uterine contraction, uterine contraction regularity, degree of cervical extension, presentation of foetal descent, the condition of intra-partum haemorrhage and postpartum haemorrhage, labour manner, lochia, involution of uterus, milk secretion, neonate Apgar Score and neonate body height and weight were also measured.

Results
Labour progress and outcome were no different between the groups, and no adverse events were observed. Pain scores from women in the EA group were significantly lower than in the control group at the end of the stimulation period (30 minutes) and 2 and 4 hours after needle withdrawal (see figure 2).

Comment
The authors do not comment on whether the effect of EA was clinically significant, as it was only about 6 mm on the VAS. In that respect, the study findings are disappointing. The authors do not report the use of any other form of analgesia such as pethidine, which would have confounded the pain scores.

Labour pain (2)


Four-arm RCT of acupuncture for labour pain relief (n=105)

Methods
A cohort of 105 nulliparae undergoing labour induction at term were randomised to 30-60 minutes of 1) 2 Hz EA (electroacupuncture) at LI4, SP6, BL60, and BL67 with sufficient intensity to cause non-painful muscle contraction; 2) manual acupuncture at the same points, with intermittent manual stimulation; 3) superficial needling to areas adjacent to these points, as ‘sham’ treatment, with half of this group also being attached to a non-functioning EA machine; 4) usual care only.

The primary end point was the rate of intrapartum epidural analgesia, and the secondary end points were parental analgesia requirement, labour length, delivery mode, neonatal condition and postpartum haemorrhage.

Results
Recruitment took 3.5 years. There were no differences in the outcomes or complications of labour or pregnancy in the four groups. For the primary outcome, epidural rates were combined for EA and manual acupuncture. The epidural rates were 65% for acupuncture, 56% for the ‘sham’ acupuncture, and 77% for the controls, with no significant differences between the groups. No side effects or complications of acupuncture were identified.

Comment
The study size was calculated on an expected effect of 50% reduction in the use of epidural analgesia – a very large anticipated effect which explains the small group size. The epidural rate in patients outside the study was about 70%. So this small study can only be interpreted as showing that acupuncture does not reduce this figure to 35%. We ask whether that was reasonable expectation? There was an insignificant trend towards higher rates of Caesarean section in the control group (35% vs 21%) and fewer instrumental deliveries (35% vs 52%). The study would have been more definitive if it had been larger, or compared just two groups.

Tinnitus


A three-armed RCT comparing manual, electro- and sham acupuncture for tinnitus (n=60).

Methods
Fifty patients (46 males) suffering from tinnitus were recruited from an acupuncture clinic. The patients were randomly assigned to three groups, each receiving six weekly treatments: a manual acupuncture group (MA), using the acupuncturist’s choice of 8-10 points from 14 (GB8, TE17, GB2, GB20, GV20, TH3, ST36) with de qi; an electrical acupuncture group (EA), points as before but with the addition of 2/100 Hz stimulation at ‘maximum below the pain threshold’; and a sham group using blunt, cut needles touching the skin and supported by elastic foam. The frequency of tinnitus, its intensity, and quality...
of life were recorded. Tinnitus matching was attempted but unsuccessfully due to variable hearing loss.

Results
There were no significant differences between groups, figure 3. Within groups, significant effects were seen from EA for tinnitus episodes and tinnitus loudness (P<0.009); and significant effects on quality of life (P<0.038) and global assessment (P<0.011) in both the EA and manual acupuncture groups.

Comment
The authors explained the lack of effects by the restriction on points selected, but there are two other relevant comments. Acupuncture can produce the occasional dramatic effects in individual patients with tinnitus (like some other conditions e.g. spinal cord injury pain). Conventional RCTs where the results of a group are combined simply miss these events, which are nevertheless important for patients. Secondly, there was evidence of trends in favour of EA in all four subjective outcome measures, so there may have been a group effect that this study was too small to detect.

Tamoxifen-induced flushes

A sham-controlled RCT of acupuncture for tamoxifen flushes (n=84)

Methods
Eighty-four patients at the Karolinska Hospital in Sweden who were taking tamoxifen for breast cancer and were suffering hot flushes of at least 50% severity were randomized to receive either true acupuncture or sham acupuncture control, twice a week for 5 weeks. Eight points were needled; LI4, HT6, LR3, ST36 unilaterally and SP6 and KI7 bilaterally, inducing de qi with 20 minutes’ needle retention. The control group received stimulation with non-penetrating Park needles 1 cm away from these points. Seventy-four patients were treated according to the protocol.

Results
In the true acupuncture group 42% (16/38) reported improvements in hot flushes after 6 weeks compared to 47% (17/36) in the control group (95% CI, -28 to 18%), figure 4. At 18 weeks the hot flush scores were virtually identical. Both groups reported improvement regarding severity and frequencies in hot flushes and sweating episodes, but there was no statistical difference between the groups. In a sub-analysis of severity of night sweats, a statistically significant difference of P = 0.03 was found in favour of the true acupuncture group. Former experience of true acupuncture did not influence the perception of true acupuncture or sham. In addition, no significant differences in hormonal levels were found before and after treatment.

Comment
Ten treatments should have been an adequate course. There was a 30% reduction in hot flush scores. The literature on sham-controlled RCTs of acupuncture for hot flushes in this troublesome condition now includes two negative studies and one positive.

Hot flushes in men

Uncontrolled (observational) study of hot flushes in men (n=22) on hormonal therapy for prostate cancer

Methods
Men who had had bilateral orchiectomy, gonadotropin-releasing hormone agonist or antagonists with or without anti-androgen therapy and had a hot flush score > 4 who were receiving androgen deprivation therapy for prostate cancer. Hot flush score is the product of number of flushes per day and severity. They underwent acupuncture with electrostimulation twice weekly for 4 weeks, then weekly for 6 weeks, using a predefined treatment plan: bilateral needling of GB34, BL15, BL23, BL32 with low frequency 2 Hz electrostimulation of the last two pairs; and unilateral needling of GV20, HT7, FC6, LR2, SP6. Needles were in place for 30 minutes with manual stimulation every 10 minutes. Dietary advice was also given, to restrict intake of caffeine, spicy foods and alcohol.
The primary endpoint was a 50% reduction in the hot flush score after 4 weeks of therapy, calculated from the patients’ daily hot flush diaries. The hot flush-related quality of life and sleep quality was assessed. Biomarkers potentially related to hot flushes were measured, including serotonin, calcitonin gene-related peptide (CGRP), and urinary 5-hydroxyindoleacetic acid, were examined.

Results
A total of 25 men were enrolled, of whom 2 were ineligible and one dropped out. After 4 weeks, 9 (41%) of 22 patients had had at least 50% reduction in the hot flush score. Twelve (55%) met this response definition at some point during the therapy course. The overall mean reduction was to 60% of baseline at 4 weeks, and 52% at 8 weeks (see Figure 5). One patient had an increase in hot flush score on one occasion during therapy. A reduced hot flush score was associated with improvement in the hot flush score on one occasion during therapy. A reduced hot flush score was associated with improvement in the hot flush-related quality of life and sleep quality (p=0.002). Quality of life according to SF36 showed no significant changes.

Serotonin levels were unchanged. Urinary 5-hydroxyindoleacetic acid and serum CGRP levels showed a trend towards reduction in those who responded.

Comment
Hot flushes in men with this condition are difficult to treat. The authors argue that these results were better than the average mean response to placebo of 25% in placebo-controlled trials, and therefore that new studies of acupuncture for hot flushes in this population are warranted.

Acupuncture safety in 2010

Haemopericardium

A 55-year-old woman presented to her local hospital 30 minutes after receiving acupuncture for myalgia and dyspepsia from an unlicensed acupuncturist in Korea. The points used were 3 cm either side of the midline 5 cm superior to the xiphisternum, (possibly ST16, Ed); and in the epigastrium, (possibly SP16, Ed). She had rapid respiratory and arterial blood gas analysis showed hypoxemia and metabolic acidosis. Chest X-ray showed pneumothorax which was drained. A chest CT scan and echocardiography then revealed a haemopericardium. An emergency pericardiocentesis, using an approach from below the xiphoid, was immediately and successfully performed in the emergency department. She was discharged 6 days later without complications.

This case deserves the attention not only of acupuncturists, but also of emergency physicians who should be aware of acupuncture-related complications, especially haemopericardium, and the necessity of rapid diagnosis and management; and of acupuncturists to remember anatomy.

Skin infection


Three cases are reported of primary inoculation tuberculosis resulting from illegal acupuncture. Three patients over 70 years old presented with erythematous, ulcerative, indurated plaques on the back. Skin lesions had developed at the acupuncture sites 1 or 2 weeks after a session of acupuncture, which was intended to relieve back pain. An unlicensed, non-medically trained person conducted each session. Granulomatous inflammatory infiltration and acid-fast bacilli were observed histologically. M. tuberculosis was identified by mycobacterial culture and polymerase chain reaction. Nine months after the initiation of antituberculosis medication, skin lesions improved, and no evidence of recurrence or other organ involvement was observed at the 1-year follow-up visit.
fully treated with the appropriate proper drug combination.

Necrotising fasciitis


An 84-year old man non-diabetic was having regular acupuncture for spinal pain. Ten days before presentation, sterile needles were inserted into the groin where he developed a large local abscess. Infection spread to the thigh and buttock, where CT scan revealed gas. Enterococcus faecalis was cultured. With surgical debridement, intensive support and intravenous antibiotics he recovered and received a split thickness graft 2 months later.

Systematic Review

Effect size of sham acupuncture


A meta-analysis (n=37 trials) investigating the size of non-specific effects associated with acupuncture.

Methods

Randomized trials of acupuncture for any condition, including both sham and no acupuncture control groups. Pooled standardized mean differences were calculated using a random effects model with the inverse variance method.

Results

Thirty-seven trials with a total of 5754 patients were included, and varied greatly regarding patients, interventions, outcome measures, methodological quality and effect sizes. As shown in figure 6, among the 32 trials reporting a continuous outcome measure, the random effects standardized mean difference between sham acupuncture and no acupuncture groups was -0.45 (95% CI, -0.57, -0.34; I² = 54%). The effect on chronic pain was larger, -0.53 (CI 0.067, -0.39). Trials with larger effects of sham over no acupuncture reported smaller effects of acupuncture over sham intervention than trials with smaller non-specific effects (b = -0.39, P =0.029).

Comment

The authors have recently demonstrated that sham acupuncture is more effective than other physical placebo interventions.1 What is the size of this effect?

‘Standardised mean differences can be interpreted the same way as the better known ‘effect size’ of the treatment, and effect sizes of 0.4 to 0.7 are usually classed as ‘moderate’. The total overall effect of acupuncture (specific and non-specific) is clinically relevant, and ‘at least moderate’ in size. Given the mixture of studies here, the effect is probably about 0.6 for painful conditions, and about 0.4 of this can reasonably be attributed to the non-specific effects.

Figure 6 Pain score, sham acupuncture against usual care (reproduced with permission of the copyright holders).

A sample of over 800 patients would be needed to show an effect of acupuncture over sham acupuncture reliably.

REFERENCE


Basic research

Experimental pain


This study assessed manual acupuncture on experimental pain parameters in 12 healthy volunteers.

Methods

The experimental design was a repeated-measures, three-group pre- and post- procedure. 12 healthy young men (mean age 21.3±2.6 years) participated in a control, sham, and acupuncture procedure, one week apart, in a counterbalanced sequence to forestall an order effect. The pain parameters assessed included the nociceptive flexion reflex (NFR) which includes the pain threshold to electrical stimulation of the ankle, and electromyographic (EMG) measurement of the response of the biceps femoris. The electrical stimulus was increased in 20V steps until the pain threshold is reached. The nociceptive reflex threshold is known to be a reliable measure of the experimental pain threshold. The nociceptive reflex amplitude on EMG was also measured.

The manual acupuncture procedure was performed at two bilateral acupuncture points, LI4 (an extrasegmental point) and ST44 (a segmental point). De qi was elicited and the needles remained in position for 20 minutes. The sham procedure was performed with the needle inserted bilaterally 1-1.5 cm outside each point. The control procedure consisted of a quiet rest for 20 minutes.

Results

Repeated-measures analysis of variance between pre- and postcontrol, sham, and acupuncture procedures for pain threshold, nociceptive reflex threshold, and nociceptive

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reflex amplitude revealed no significant difference (see figure 7).

Comment
It has been shown previously that the NFR threshold is inhibited by electroacupuncture. So this study points up the differences between manual and electrical stimulation – they are different qualitatively, not just quantitatively. They have different inputs at the spinal segmental level, and therefore probably need to be given at different points for a given effect. The authors comment that the choice of ST44 (dorsum of foot) might not have been appropriate for the biceps femoris. Consideration of the acupuncture points’ dermatomes and myotomes supports this: the dermatomes of forefoot and hamstrings are similar, but their myotomes differ, being S2/3 for ST44 and L3/4 for the hamstrings.

Imaging long-term changes


Background
The authors argue that there are two effects of acupuncture: responses to the tissue injury effect at the time of needling, and then prolonged, subtle, network responses that continue to generate pain relief after the needles have been removed.

The accumulating evidence from neuroimaging studies in humans has shown that acupuncture can modulate a widely distributed brain network, large portions of which overlap with the pain-related areas. A striking feature of acupuncture-induced analgesia is its long-lasting effect, which has a delayed onset and gradually reaches a peak even after acupuncture needles are removed. Identifying neural responses over time may shed light on how such peripheral inputs are conducted and mediated through the CNS.

The present study used a non-repeated event-related (NRER) fMRI paradigm and control theory based approach namely change-point analysis in order to capture the detailed temporal profile of neural responses induced by acupuncture at ST36.

Results
The findings demonstrated that neural activities at the different stages of acupuncture presented distinct temporal patterns. Consistently positive neural responses were found during the period of acupuncture needling, while much more complex and dynamic activities were found during the post-acupuncture period. These brain responses had a significant time-dependent effect which showed different onset time and duration of neural activities.

The amygdala and perigenual anterior cingulate cortex (pACC), exhibited increased activities during the needling phase while decreased gradually to reach a peak below the baseline. The periaqueductal gray (PAG) and hypothalamus presented saliently intermittent activations across the whole fMRI session.

Apart from the time-dependent responses, relatively persistent activity was also identified in the anterior insula and prefrontal cortices. The overall findings indicate that acupuncture may engage differential temporal neural responses as a function of time in a wide range of brain networks.

Comment
fMRI studies so far have mostly been limited to acute changes, and have been surprisingly inconsistent. As experience and techniques of imaging improve, so we expect increasing information about the long-term changes seen with acupuncture. The complex modulations of temporal neural response are more relevant to clinical changes in patients.

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