Summaries of recent papers

Clinical trials of effectiveness

Acute migraine attack: randomised controlled trial


Sham-controlled randomised controlled trial (RCT; n=150) for the treatment of acute migraine.

Methods

A total of 150 patients with acute migraine were recruited from 5 different hospitals over 2 years, and randomly allocated to verum or sham acupuncture.

Both groups received one session of acupuncture treatment of 30-min duration. In the verum group, the obligatory points included GV20, GV24, ST8, GB8 and GB20. According to different syndromes additional points could be chosen. The sham group were randomly allocated to one of five groups of different sham points, two on the arms and three on the legs unrelated to headache treatment, and at least 3 mm away from the correct site of acupuncture points. All needles were manually stimulated to elicit de qi. Acupuncture treatments were given by experienced acupuncturists who had received special training to improve consistent practice throughout the different hospitals.

The trial was single (participant) blinded. The primary outcome measure was between-group difference in visual analogue scale (VAS) score for pain after 24 h. There were several secondary outcome measures.

Results

The VAS pain scores decreased in both groups, (figure 1) with significant differences between the two groups (p=0.001). The secondary outcomes also showed a reduction in both groups, including function, acute medication intake, accompanying symptoms, pain freedom and recurrence of migraine, although not all outcomes showed statistically significant differences between the two groups.

Comments

Although the primary outcome of reduction in pain VAS score showed a statistically significant difference between the groups, both groups showed an improvement. Sham needling cannot be assumed to be physiologically inert, and has benefits through the diffuse noxious inhibitory control and descending inhibitory pain pathways. The authors acknowledge that the VAS score should also have been measured at 2 h post treatment, which is used to assess acute migraine treatment with drugs, to allow a comparison in treatment options.

I am unsure how applicable the findings are, as most patients would perhaps struggle to access acupuncture treatment quickly enough to treat their acute migraine by such means in comparison with standard drug therapy.

Nausea and vomiting in paediatric chemotherapy


Randomised crossover-design feasibility study (n=10) comparing auricular point pressure to sham.

Methods

Children undergoing chemotherapy for leukaemia or solid tumours were randomised to have seeds to apply pressure with taped to their ears, either at proper auricular points, or at sham points, following chemotherapy. They were asked to apply pressure three times daily, plus when required for nausea. They were switched to the other trial arm following their next chemotherapy session. A modified Morrow Assessment of Nausea and Emetics score was used to measure response. The study was too small to assess efficacy, but was conducted to: test feasibility of recruitment into a trial, acceptability of treatment protocol, analyse longitudinal data and determine the size for a future trial. All children were allowed to have antiemetics as well.

Results

Out of 17 children who were enrolled, 10 completed the trial. The mean age was 13 years (range 6–18 years). Reasons for dropping out were change of treatment regimen, need for a bone marrow transplant and one child refused to complete the trial. Out of 140 participant days, seeds were in place for 123 days (88%). A reduction in nausea and vomiting was found in both acupressure groups (figure 2), with no statistically significant

![Figure 1](image-url) Migraine pain visual analogue scale (VAS) scores. Based on Wang et al. Pain Med 2012;13:623–30.
difference between the two groups. The authors concluded that enrolment into a trial was feasible, but that a larger trial of 315 patients was needed to determine efficacy.

Comments
This trial was not designed to demonstrate efficacy of auricular acupressure. Such a trial would need more participants, a different design and perhaps a different or additional control group: correct and sham points were in close proximity, often in the same area of innervation, and it is difficult to accept that the sham in this trial may be accepted as an inactive placebo. Also, a description of the randomisation process would be important: it was absent from this paper.

Radiation-induced nausea


A sham controlled RCT (n=237) for radiotherapy-induced nausea and vomiting.

Methods
A total of 237 adults were included who had an abdominal or pelvic tumour and were to receive radiotherapy. Patients who had experienced nausea and vomiting 24 h before treatment or had received acupuncture treatment during the prior year were excluded. Patients were randomised to either verum or sham acupuncture. The verum group received acupuncture treatment bilaterally to PC6 for 30 min with three manipulations to elicit de qi. Sham acupuncture was administered bilaterally to a non-acupuncture point 2 cun proximal to PC6 using a telescopic ‘Park’s sham device’, again for 30 min and manipulated three times. The procedures were performed three times a week for the first 2 weeks, then twice a week for the duration of the radiotherapy period.

The primary outcome was the proportion of patients ‘experiencing nausea’ during the whole period of radiotherapy treatment. Secondary outcome measures included the number of days with nausea, the intensity of nausea and the proportion of patients vomiting. In addition a subgroup analysis of patients receiving chemotherapy was performed.

Results
A total of 197 patients completed the study. No statistically significant differences in nausea were noted between the verum and sham acupuncture groups (figure 3). Furthermore there was no difference noted in the secondary outcomes or subgroup analysis of patients receiving

Figure 2 Occurrence of nausea and vomiting. SC, standard care; AAP, auricular acupressure; SAP, sham.

Figure 3 Patients (%) experiencing nausea and vomiting each week. Based on Enblom et al. Ann Oncol 2012;23:1353–61.
chemotherapy. Subjectively, patients in both groups reported that they believed the acupuncture treatment was effective in treating nausea. In all, 67% in both groups reported positive effects on mood, sleep and pain reduction and 89% in both groups wanted to receive acupuncture treatment again.

**Comments**
This paper investigates the use of acupuncture in managing the side effects of radiotherapy; most work has been published in acupuncture for chemotherapy-induced nausea. The study seems to show a convincing negative result, which is challenging. While the sham group did not involve penetration, it was not performed at the same point as the verum acupuncture treatment procedure. It may have been more informative to have used the sham needles at the PC6 site. The subjective evaluations of the patients are difficult to assess as it is not apparent as to what they are comparing these perceived effects to. A non-acupuncture control group would have allowed better interpretation of whether the interventions were equally effective or equally ineffective.

**Chronic obstructive pulmonary disease**
Sham-controlled RCT (n=68), focusing on dyspnoea on exercise (DOE).

**Methods**
A total of 68 patients from Japan who were diagnosed as having chronic obstructive pulmonary disease (COPD; stages II–IV) and who were receiving standard medication were randomly assigned to traditional acupuncture (real acupuncture group, n=34) or placebo needling (placebo acupuncture group, n=34). Both groups received real or placebo needling (Park device) once a week for 12 weeks at LU1, LU9, LI18, CV4, CV12, ST36, KI3, GB12, BL13, BL29 and BL23.

The primary end point was the modified Borg scale score evaluated immediately after the 6-min walk test. Measurements were obtained at baseline and after 12 weeks of treatment.

**Result**
After acupuncture, the Borg scale score at the end of the 6-min walk test was significantly better in the real acupuncture group compared with the placebo acupuncture group (figure 4). The mean difference was −3.58 (−4.27 to −2.90). The real acupuncture group also experienced improvement in the 6-min walk distance, indicating better exercise tolerance and reduced DOE; and increased PaO2 and range of movement of the rib cage.

**Figure 4** Borg scores. Based on Suzuki et al. *Arch Intern Med* 2012.

**Comments**
Blinding of participants was good, and the staff involved in measurements were also blinded. The outcomes included subjective scores and other measurements that are reasonably objective. Therefore we can have confidence in the improvement in the Borg score, which was clinically significant. This is the first positive sham-controlled study of acupuncture in COPD. The authors (who recently reported a case series of COPD in this journal) made a point of the care taken in training the acupuncturists to use the Park device. The authors speculate that the mechanisms could be via improved neuromuscular function of the respiratory muscles.

**Stroke recovery**
RCT (n=62) in patients with long-term stroke issues.

**Methods**
A total of 62 subjects who had an ischaemic stroke at least 18 months previously and were moderately but not severely affected were randomised to receive 10 half-hour sessions, twice weekly, of placebo or active low-frequency electrical stimulation (2/100 Hz) using subcutaneous acupuncture needles over the scalp. The intensity was noticeable but bearable. The following areas were stimulated contralaterally: (a) motor area of the face: upper limb, lower limb, (three needles); (b) sensory correspondent areas: face, upper limb, lower limb (three needles); (c) sensory-motor area of the lower limbs (bilateral) (two needles); (d) supplementary motor area (three needles); (e) language area (only for right hemiplegia) (three or more needles). In the placebo group, non-functioning electric wires were fastened to the scalp in the same locations.

Functional and neurological evaluations were indexed by the Barthel, Rankin, and National Institutes of Health Stroke Scale (NIHSS) instruments.
Results

Results (figure 5) show that there was a significant difference in functional improvement between the sham and active group as measured by NIHSS but not by the other two scales (Rankin and Barthel).

Comments

Was this trial positive or negative? Is there any reason why the NIHSS instrument could show an effect when the other measures did not? The authors argue that the NIHSS has more components so is likely to be more sensitive to change, especially neurological components that might respond quite quickly but take some time to feed through into the other two scales, which are designed to assess the level of assistance needed. But they do not provide any supportive references for this argument. This result seems to justify larger studies, because the potential benefit is important.

Atrial fibrillation


Two studies: RCT (n=80) after cardioversion; and observational study (n=31) in paroxysmal atrial fibrillation (AF).

Methods

A. In the first study, a group of 80 patients with persistent atrial fibrillation (AF) on anticoagulants who had received electric cardioversion were randomised to verum acupuncture, sham acupuncture or no treatment groups. A non-randomly assigned amiodarone-treated group was used as a reference group.

B. The second study group consisted of 31 patients who had frequent symptomatic paroxysmal AF for the previous 6 months. All patients were given verum acupuncture treatment.

All patients in both groups had preserved ventricular function. Patients with ischaemic heart disease, cardiomyopathies, inflammatory disease and renal, hepatic or thyroid disease were excluded.

Acupuncture treatment consisted of needling points PC6, HT7 and BL15 for 10–20 min, weekly for 10 weeks. No details of the sham acupuncture were given.

The primary outcomes were recurrence rate for the persistent AF study and number and duration of AF episodes for the paroxysmal AF group, over 12 months.

Results

A. In the persistent AF study group, verum acupuncture was shown to reduce the recurrence rate compared with the sham acupuncture and control group (35% vs 69% and 54% respectively). The amiodarone reference group had a recurrence rate of 27%. The statistical significance of these results was not reported. Combined relapse rates are shown in figure 6.

B. The paroxysmal AF study showed a statistically significant reduction in the number (p=0.0009) and duration of episodes (p=0.0001) of symptomatic AF episodes at 2 and 12 months after the start of acupuncture treatment compared with the (historical) control non-treatment period.

Comments

AF is the most common sustained cardiac arrhythmia, and a challenge and burden to healthcare systems. Little has been previously reported on the use of acupuncture in its management. These are essentially preliminary reports. Persistent AF treated with electric cardioversion has high recurrence rate (approximately 70% at 1 year) and hence any treatment that may reduce this would be valuable clinically. The study shows that acupuncture may have a therapeutic effect, however the methods of this study are unfortunately incompletely described. A description of the sham acupuncture procedure is not given, and this is known to have a significant effect on outcome. Furthermore the amiodarone treatment group was not randomly assigned; instead it was a reference group. Ideally all patients should have had an equal chance of receiving all treatments including amiodarone. The paroxysmal AF study unfortunately did not have a control group and used the pre-acupuncture period as its control. While this can have merit, AF is a dynamic process that
changes over time hence a concurrent control group would have been more rigorous. This paper presents interesting results that deserve further controlled trials.

**Systematic reviews**

**In-vitro fertilisation (1)**


**Methods**

Seven databases were searched for RCTs of acupuncture in women undergoing in vitro fertilisation (IVF). In all, 31 trials were identified, of which 24 (n=5807) were included in the analysis. The data were presented for all trials combined, but also separately for trials that used the Streitberger needle as a control and those that did not (superficial acupuncture, needling at non-traditional points). All forms of acupuncture, including laser, were included.

**Results**

Acupuncture was effective for achieving a pregnancy (OR 1.22, 95% CI 1.01 to 1.47), but the effect was not significant for achieved live births OR 1.09, 95% CI 0.7 to 1.60). It was significant for both outcomes when analysis included only non-Streitberger controls (pregnancy OR 1.34, 95% CI 1.03 to 1.67; birth OR 1.63, 95% CI 1.16 to 2.30), see figure 7. But control was favoured in trials that used the Streitberger needle (pregnancy OR 0.89, 95% CI 0.78 to 1.09; birth OR 0.74, 95% CI 0.58 to 0.95). The authors suggested that the Streitberger needle may not be an inactive procedure, leading to underestimation of the acupuncture effect. Best pregnancy rates were achieved when acupuncture was given at the time of controlled ovarian hyperstimulation or oocyte aspiration, but less so at time of embryo transfer.

**Comments**

There have been previous systematic reviews in this topic, and this study has included more recent trials. Their approach to search and inclusion of trials is logical and clear. It should be noted that pregnancy rates were available from 23 trials, but live birth rates from only 6. The authors have included studies that were not designed to assess pregnancy rates as outcome, but pain relief for the IVF procedures. They also included a large number of outcome measures, which are not all clear; surely, a confirmed pregnancy and a live birth are more than enough outcome parameters. Finally, while it is not possible here to review the debate about controls for acupuncture studies, the authors seem to overlook the possibility that the non-penetrating Streitberger control may give a more accurate assessment of efficacy of needle penetration, whereas the other controls may overestimate the acupuncture needle effect.

**In vitro fertilisation (2)**


Systematic review, 17 trials.

**Method**

A total of 11 databases were searched for RCTs relating to acupuncture and IVF. In all, 62 trials were identified, of which 17 papers (n=3713) were included. Acupuncture could be traditional, auricular, electroacupuncture (EA) or
laser acupuncture. Eligible trials had to have extractable data on any marker of confirmed pregnancy, including miscarriage.

Results
For clinical, biochemical and ongoing pregnancy outcome, implantation rate and live birth outcome there was statistically significant heterogeneity and no significant difference between the acupuncture and control groups in outcomes. For example, the risk ratio for pregnancy was RR=1.09 (95% CI 0.94 to 1.26). For the miscarriage outcome, there was no statistically significant heterogeneity, and no significant difference between the acupuncture and control groups. The review concludes that, although no statistically significant benefit of acupuncture had been demonstrated, there was a trend towards a more favourable outcome in the acupuncture groups and further larger sized, multicentred, traditional Chinese medicine-based trials should be conducted before a final decision is made.

Comments
No information was included regarding which trials used which type of acupuncture for the treatment, or which points were commonly used. Likewise, no description was given as to the type of sham acupuncture used. It seems unjust to combine all forms of acupuncture together to draw any conclusions on all acupuncture treatment effects, which is compounded by not knowing the type of sham or control used.

Three out of five previously published systematic reviews and meta-analysis between 2008 and 2009 showed a significant improvement in IVF outcomes. However, since this time there have been more than 10 newly published RCTs, perhaps justifying this further systematic review. The larger of these trials did not find any significant difference between acupuncture and sham treatments.

The authors comment on the high degree of heterogeneity between the trials, and offer several explanations for this occurrence. A random effects model was used where this was encountered, but it seems unlikely that this will counteract this degree of heterogeneity, making it difficult to draw meaningful conclusions from this review.

The evidence in figures 7 and 8, taken together, does not give a convincing picture that acupuncture at the time of oocyte retrieval or embryo transfer increases live births: allowing for a bit of bias, the results seem evenly spread. Also, for most conditions, acupuncture is superior to no acupuncture, and this is usually interpreted as a placebo response: that is not true for infertility.

Irritable bowel syndrome


Methods
Analyses were presented for acupuncture compared with sham acupuncture, with medication, with *Bifidobacterium*, with psychotherapy, as an adjunct to other treatments and to usual care alone.

Results
In all, 17 RCTs (N=1806) were included. Acupuncture was not superior to sham acupuncture for symptom severity (standardised mean difference (SMD)=−0.11, 95% CI −0.35 to 0.13) or quality of life (SMD=−0.03, 95% CI −0.27 to 0.22).

As shown in figure 9, acupuncture was more effective than medication (RR of symptom improvement=1.28, 95% CI 1.12 to 1.45). It was also superior to no specific treatment.
treatment (RR=2.11, 95% CI 1.18 to 3.79). There was no difference between acupuncture and *Bifidobacterium* or between acupuncture and psychotherapy. Acupuncture as an adjuvant to another Chinese medicine treatment was statistically significantly better than the other treatment alone, in trials with a high risk of bias (RR=1.17, 95% CI 1.02 to 1.33; four RCTs).

**Comments**

Any effect of acupuncture in irritable bowel syndrome is likely to be a general effect of neuromodulation, not a segmental effect, and certainly not point specific. So it is not surprising that sham-controlled RCTs showed no benefits of acupuncture. It might require 800 participants to show an effect, and only 331 were available for this analysis. More relevant to clinical practice is the finding that acupuncture is superior to medication and useful as an adjunct. These studies were not blinded of course, but that would be impossible.

**Expectancy**


**Methods**

Expectancy has been suggested to be a key component of the placebo response. After conducting a thorough literature search, the authors identified nine studies that reported the relationship between expectancy and treatment response to acupuncture.

Most of the studies concerned pain-related conditions. Participants were acupuncture naive in six of the studies, and in another two they had not received acupuncture for the condition under study. Electroacupuncture was used in five studies, manual acupuncture in three studies and one study investigated placebo acupuncture. Simple assessment of expectancies on Likert-like scales (eg, a five-point scale ranging from ‘strongly agree’ to ‘strongly disagree’) was carried out in five studies. Expectancies were manipulated in the remaining four studies by randomising patients to receive information to enhance expectancies or neutral/negative information.

**Results**

The heterogeneity of the studies precluded the possibility of a meta-analysis being carried out. Instead this descriptive review of nine studies showed mixed results with five of the studies finding at least some evidence of statistically significant effects of expectancy on acupuncture outcomes, whilst the remaining four failed to do so.

Those studies investigating experimentally-induced pain, those that manipulated expectation and those involving electroacupuncture were the most likely to find a relationship of expectancy on acupuncture outcomes. However, it was more likely for studies on experimentally-induced pain to manipulate outcomes and to use electroacupuncture, so that it is not possible to establish the individual contribution of each of these three components. However, the largest study on a clinical outcome that assessed expectancies and that involved manual acupuncture also found a significant relationship. In fact, the two largest studies in terms of sample size, and therefore likely statistical power, measured clinical outcomes and found a significant relationship between expectancy and outcomes.

All but one of the studies had some risk or unclear risk of bias.

**Comments**

Acupuncture is a complex intervention with many components that may contribute to its overall effect. Despite its limitations, this systematic review provides at least some evidence that expectancy may well be one of these components. The authors suggest that future studies would be more informative if they manipulate and assess expectancies. Research can further be made more objective by the systematic development of a valid instrument for measuring expectancies in order to enable comparisons across studies.

**Research methodology**

**Debriefing sham/placebo group participants**

Acupuncture research update

Summary
Participants in placebo-controlled clinical trials give their informed consent to be randomised to verum or placebo groups. However, at the end they are rarely told which treatment they actually received. Debriefing those randomised to placebo could have negative consequences: it might induce relapse, could undermine further therapeutic relationships and could have negative psychological consequences, though there is little evidence for any of these consequences.

Four participants who had completed a trial of acupuncture or sham acupuncture (Streitberger needle) for irritable bowel syndrome were interviewed and debriefed. All had responded to the intervention. All were convinced they had had real acupuncture, described feeling the needles clearly penetrating the skin. They were shocked to learn that they had been given placebo. One refused to believe this had been placebo and thought there must be some mistake. The others reattributed their improvement to the supportive and psychological effects of the acupuncturist, recognising the fact that irritable bowel syndrome is related to stress. All were pleased to have participated in the trial from which others would benefit.

The authors point to need for further studies on debriefing the placebo group, and suggest ways in which debriefing to placebo allocation can be managed sensitively to facilitate positive outcomes for participants.

Basic research

Hyperalgesia

RCT (n=72) investigating the synergy between amitriptyline and electroacupuncture.

Methods
Only rats that had previously been found to be responsive to EA analgesia were included in this study. Threshold to mechanical stimulation (MS) was measured with an electronic von Frey apparatus before and after incision of the plantar surface of the right hind paw. Needles were inserted in ST36 and SP6 and stimulation was applied at 2 Hz or 100 Hz for 20 min. Needles were inserted but not stimulated in the sham EA groups that served as controls. Groups of six rats each were subjected to intraperitoneal or intrathecal amitriptyline or saline control. Outcome measures used were (a) threshold to MS and, (b) tail-flick latency (TFL), measured at regular intervals afterwards.

Results
TFL gradually increased in saline-treated rats receiving EA but not sham EA, with the effect of EA at 2 Hz lasting longer than EA at 100 Hz.

Figure 10 Amitriptyline prolongs the antihyperalgesic effect of electroacupuncture (EA). Based on Fais et al Eur J Pain 2012;16:666–75.

Amitriptyline significantly increased the effects of 2 Hz and 100 Hz EA on post-incision hyperalgesia compared to saline with the maximum effect of 100-Hz EA being achieved more quickly than with 2-Hz EA.

Amitriptyline also increased the intensity of the antihyperalgesic effect of 100-Hz EA on incised and non-incised paws, but not of 2-Hz EA.

The EA-induced antihyperalgesic effect lasted longer with amitriptyline than with saline with the effect being stronger with 100-Hz EA (see figure10).

Comments
Acupuncture and amitriptyline are both thought to influence pain through their effects on the descending serotonergic and adrenergic inhibitory central nervous pathways; acupuncture at midbrain level, amitriptyline in the spine. This experiment specifically highlights the synergistic effect of these modalities in the context of postoperative pain. In addition, it provides support for their combined use in the more challenging field of chronic pain in which hyperalgesia is a common finding.

Competing interests None.

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