A randomised study comparing the effectiveness of acupuncture or morphine versus the combination for the relief of dyspnoea in patients with advanced non-small cell lung cancer and mesothelioma

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Original Research

Abstract  Background: Dyspnoea is one of the commonest symptoms of lung cancer. Opioids can reduce dyspnoea. This study investigates acupuncture for relief of breathlessness in lung cancer.

Methods: We performed a single-centre, randomised phase II study of 173 patients with non-small cell lung cancer or mesothelioma with dyspnoea score of ≥4 on visual analogue scale (VAS). Randomisation was to acupuncture alone (A), morphine alone (M) or both (AM). Acupuncture was administered at upper sternal, thoracic paravertebral, trapezius trigger points and LI4. Manubrial semi-permanent acupuncture studs were inserted and massaged when symptomatic. Arm A patients received rescue morphine. Primary end-point was proportion of patients achieving ≥1.5 improvement in VAS dyspnoea at 4 h. Measurements continued to day 14 and included VAS relaxation, line analogue rating (Lar) anxiety, hospital anxiety and depression and European Organisation for Research and Treatment of Cancer quality-of-life scores.

Results: Dyspnoea VAS improved ≥1.5 in 74%, 60% and 66% of arms A, M and AM, respectively, and was maintained in 45% at 2 weeks. There was no statistically significant difference between arms. VAS relaxation improved in arms A (1.06 points) and AM (1.48 points) compared to arm M (−0.19 points, p < 0.001). At 7 d, the Lar anxiety score improved in arm A (1.5 points), arm AM (1.2 points) and arm M (no change, p = 0.003). Fewer patients...
received at least one morphine dose in arm A compared with arm M or AM (21% versus 87% versus 87%, respectively, \( p < 0.001 \)).

**Conclusions:** A, M and AM were effective in relieving dyspnoea. Acupuncture relieved anxiety and was morphine sparing, providing an alternative to morphine.

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1. Introduction

Dyspnoea is one of the commonest symptoms of lung cancer [1]. Though unlicensed for treating dyspnoea, oral and parenteral morphine are commonly used [2]. Unfortunately, patients may develop toxicities such as constipation, nausea and respiratory depression.

One study of cancer patients reported that 64% used complementary therapy [3]. Patients use acupuncture to manage pain, side-effects and stimulate the immune system [4–7]. Acupuncture is widely provided in oncology units and hospices [8].

The majority of trials of acupuncture for breathlessness have been performed in a non-cancer setting. A trial of traditional Chinese acupuncture in chronic obstructive pulmonary disease (COPD) demonstrated improved breathlessness and 6-min walk test compared to placebo [9]. Others have shown superiority of acupuncture over placebo in COPD on Borg dyspnoea scores and 6-min walk [10]. Trial of Wu et al. [11] in COPD randomised to active acupressure (non-needle pressure to acupuncture points) or sham acupressure and showed that the former significantly improved pulmonary function, dyspnoea and 6-min walk. A Cochrane review of non-pharmacological interventions for breathlessness included five trials of acupuncture, though only one of these included cancer patients. The trials were heterogeneous and small and the review found insufficient evidence to recommend acupuncture [12].

A pilot study of 20 cancer patients by Filshie et al. [13] suggested that acupuncture gave short-term benefit. Seventy percent of patients reported symptomatic improvement, with a significant reduction on dyspnoea visual analogue scale (VAS) score 6 h post-acupuncture. To prolong response, the authors proposed acupuncture studs. These indwelling upper-sternal needles can be massaged by the patient when dyspnoeic or prior to exercise.

Data are accumulating on acupuncture mechanisms of action. Endogenous endorphin release is important and some effects of acupuncture are inhibited by naloxone [14,15]. Zhao [16] summarised other mechanisms of action, including serotonin release.

This study investigates acupuncture for relief of breathlessness in patients with advanced lung cancer.

2. Methods

2.1. Trial design

Eligible participants recruited from out-patient clinics had a histological diagnosis of non-small cell lung cancer (NSCLC) or mesothelioma and were breathless at rest with a score \( \geq 4 \) on VAS. The patient makes a mark on a 100-mm line with descriptors at each end corresponding to the extent of their symptom [17]. The line analogue rating (Lar) scale comprises 100 mm lines, with extremes of feeling at each end and a central section representing normal state of mind [18]. Inclusion criteria were Eastern Cooperative Oncology Group performance status (PS) 0–3 and no change in treatment (chemotherapy/radiotherapy) in the previous 4 weeks or change of steroids in the previous 1 week. Exclusion criteria included acupuncture in the previous 4 weeks, acupuncture contraindications, current morphine use or reversible causes of breathlessness (including anaemia or pleural effusion).

Subjects were randomised using permuted blocks with stratification factors of PS and steroid use in a 1:1:1 ratio by telephone to acupuncture alone (arm A), morphine alone (arm M) or acupuncture in combination with morphine (arm AM). In Arm A, acupuncture was administered to two upper sternal midline points (12), five paraspinal points from T1 to T5, two to three trigger points in the trapezius muscle bilaterally and LI4 (acupuncture point near the base of thumb) bilaterally (Fig. 1). Thirty-millimetre-long 36-gauge stainless steel acupuncture needles (Seirin) were inserted and left in situ for 10 min. At sternal points, needles were inserted to the level of the periosteum and gently ‘pecked’ twice. No attempt was made to elicit needling sensation (‘de qi’) at other sites. After needle removal, stainless steel press needle studs (Seirin/Acumedic) were inserted in the upper 6 cm of the midline sternum to 0.6 mm and covered with a dressing. Treatments were given between 12 and 2 pm to avoid diurnal variation. Patients were instructed to massage studs for 1 – 2 min when symptomatic or prior to exercise whilst documenting in a diary. The ethics committee advised against using a placebo and that arm A should have access to rescue morphine. Therefore, all patients were given a supply of morphine with anti-emetics and laxatives. In arm M,
patients were prescribed oral morphine solution (Ora-morph) and advised to take 2.5 mg four hourly with breakthrough doses up to hourly and documented in a diary. In arm AM, patients received morphine (as for arm M) 20 min before acupuncture (as for arm A).

2.2. Data collection

Baseline assessments included full blood count, respiratory rate and lung function (forced expiratory volume in 1 s [FEV1] and peak expiratory flow rate [PEFR]). Symptoms were measured using VAS, Lar, Borg dyspnoea scale, hospital anxiety and depression (HAD) score and European Organisation for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ-30 lung-specific module). Assessments were made at 30 min, 90 min, 4 h, and days 2, 7 and 14.

2.3. Outcomes

The primary objective was to investigate whether acupuncture increased the proportion of patients having \( \geq 1.5 \) point reduction in VAS for dyspnoea at 4 h compared to morphine.

Secondary objective measures included lung function and change in symptoms such as anxiety and relaxation.

2.4. Sample size

We expected 20% of patients to achieve \( \geq 1.5 \) point improvement in dyspnoea VAS with morphine alone. For acupuncture to be clinically relevant, we sought a response rate of 50% (either alone or in combination with morphine), an aim found to be realistic in the pilot study [13]. Using the Pocock method to allow interim analyses at a significance level of 0.01 and power of 80%, it was calculated that 58 patients would be needed per arm.

2.5. Statistical analysis

The proportions of patients achieving the primary end-point were compared using the chi-square test. For secondary end-points, the changes in scores from baseline at time points were plotted. Data were tested for normality and groups compared using analysis of variance or Kruskal–Wallis (KW) test. Secondary end-point analyses were performed using a 1% significance level. Analyses were performed using SPSS Statistics version 22 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Recruitment and baseline characteristics

The trial recruited July 2006 to June 2014 (Fig. 2). Median age of the study population was 73 years. Most patients had a PS of 0–2. Baseline median dyspnoea VAS was 6.5. Groups were well balanced for main characteristics (Table 1).

3.2. Interim analyses

Interim analyses were performed between August 2009 and March 2012. As there was no significant difference in the response rate between arms, recruitment continued.

3.3. Primary end-point

Data were analysed on an intention-to-treat basis comprising all randomised patients. One hundred and
fifteen patients (66%) had a response (≥1.5 VAS dyspnoea reduction at 4 h). Response rates in arms A, M and AM were 74%, 60% and 66%, respectively. There was no significant difference between the arms (A versus M p = 0.12, M versus AM p = 0.50). Response was maintained at week 2 (45%) (Fig. 3).

3.4. Secondary end-points

Secondary end-points were analysed in the per-protocol population (158 patients) comprising all randomised patients completing baseline and at least one follow-up assessment.

3.5. Lung function tests

There was no statistically significant difference in the change from baseline respiratory rate, FEV1 or PEFR.

3.6. Total dose of morphine

Twenty-one percent of patients in arm A, 87% in arm AM and 87% in arm M took at least one dose of morphine (p < 0.001). Median total dose (in milligrams) taken over the study period was 32 (1–60) in arm A, 40.6 (3–154) in arm AM and 53 (13–163) in arm M (p = 0.007, KW test).
3.7. Acupuncture studs

There was no significant difference in the number of times acupuncture studs were massaged between treatment arms. Studs were massaged up to 32 times a day.

3.8. VAS dyspnoea

For VAS dyspnoea, a decrease indicates dyspnoea improvement. Mean reduction in the VAS dyspnoea score at 4 h was 2.62 in arm A, 2.66 in arm M and 2.86 in arm AM. There was no statistically significant difference in change from baseline between treatment arms ($p = 0.142$) (Table 2).

3.9. VAS relaxation

For VAS relaxation, a decrease indicates an improvement in relaxation. There was a statistically significant difference in change from baseline mean scores between arms ($p < 0.001$) (Table 3). Post hoc analysis with Bonferroni correction showed a mean improvement in VAS relaxation in arm A ($-1.06 \pm 2.6$) that was greater than arm M ($0.19 \pm 2.43$) in which VAS worsened ($p < 0.001$). Mean improvement in arm AM was greater ($-1.48 \pm 2.05$) than arm M ($p < 0.001$).

3.10. Borg dyspnoea

For Borg dyspnoea scale, a decrease indicates an improvement in dyspnoea. There was a significant difference in median change from baseline at 30 min ($p = 0.003$) with a one-point improvement for arms A and AM but no change for arm M. There were no significant differences at other times (Table 4).

3.11. Lar anxiety and relaxation

For Lar anxiety, an increase indicates an improvement in anxiety. A tendency towards improvement was seen in arm A (2) and arm AM (1.4) at 4 h when compared to arm M (0.1) ($p = 0.022$, not significant at 1% level), which was maintained at 7 d ($p = 0.003$) (Table 5).

For Lar relaxation, a decrease indicates an improvement in relaxation. Improvements were seen in arm A (−1) and arm AM (−0.9) at 4 h when compared to arm M (0) ($p = 0.006$). There were no significant differences at other times (Table 5).

3.12. HAD scale

For HAD, a decrease indicates an improvement in anxiety or depression. There was no interaction between

![Fig. 3. Dyspnoea response rate.](image)
the effects of treatment and time on mean change from baseline anxiety or depression scores (Table 6).

3.13. EORTC QLQ (global health)

There was a statistically significant difference in change from baseline mean global health scores between treatment arms \((p = 0.009)\) (Table 7). Post hoc analysis showed a mean change of 7.08 ± 25.54 for arm A, −2.08 ± 17.70 for arm M and 2.72 (±16.96) for AM (A versus M \(p = 0.009\) and M versus AM \(p = 0.308\)).

3.14. PS and VAS dyspnoea

Eighty-four percent of patients completed the study to 14 d. At baseline, 13% had a PS of 3. Ten in 23 (43%) of the PS 3 patients completed the study to 14 d compared to 135 of 150 (90%) of those with PS of 0–2. Nevertheless, 61% of PS 3 patients achieved an overall response rate across all three arms with a 75% response rate in arm AM.

3.15. Adverse events

Toxicity data were available for 123 patients. In arm M, 39% of patients reported side-effects (G1) such as constipation, nausea and drowsiness. One patient withdrew due to morphine intolerance. In arm AM, 35% of patients reported toxicity with constipation (G1) being the most common (33%). In arm A 1% reported toxicity (G1–2). One patient in arm AM died of progressive lung cancer. Side-effects were in line with morphine’s toxicity profile. Two cases of skin irritation were attributable to acupuncture site dressings.

4. Discussion

We completed an open, phase II randomised controlled trial investigating acupuncture in relieving breathlessness in patients with NSCLC or mesothelioma. There were no significant differences in dyspnoea control between groups and the primary end-point was therefore negative. However, all arms over-performed relative to...
original expectations with response rates of 60–74%.

The trial is unique in using a direct comparison to morphine (standard of care) and the use of indwelling studs to prolong acupuncture effect.

Our study was not blinded. Sham acupuncture techniques include needles inserted away from acupuncture points. However, insertion at any location can cause nerve stimulation. Non-penetrating needles in which the needle is retracted into the sheath so that pressure is applied without penetration have been devised [19]. While the patient is expecting that this is an active procedure, a response is generated via the ‘limbic touch response’ [20]. A positron emission tomography scanning study using non-penetrating needles (with the expectation they were receiving acupuncture) showed activation of cortical areas and midbrain greater than seen with inert controls but less than with acupuncture [21]. The placebo effect is well recognised in non-pharmacological and drug treatments [22]. Vickers et al. [23] conducted a pilot study in cancer patients.

Forty-seven patients were randomised to a session of acupuncture (followed by acupuncture studs) or placebo acupuncture (followed by acupressure studs). Whilst the results were negative, there were study limitations with higher dyspnoea scores in the acupuncture group and the sham treatment group having one real acupuncture stud inserted.

Rescue morphine was not provided to arm A patients until 4 h and therefore would not have affected the primary end-point. Twenty-one percent of arm A patients took rescue morphine. Of these, four (36%) were non-responders at 4 h, and only one (9%) became a responder after taking morphine.

Table 5
Median (range) change from baseline for Lar relaxation and anxiety at follow-up by treatment.

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm M</th>
<th>Arm AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lar anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 h</td>
<td>2 (−3.7 to 7.3)</td>
<td>0.1 (−3.6 to 4.3)</td>
<td>1.4 (−3 to 5.9)</td>
</tr>
<tr>
<td>Day 7</td>
<td>1.5 (−2.5 to 8)</td>
<td>0 (−4 to 6.2)</td>
<td>1.2 (−5.4 to 6.3)</td>
</tr>
<tr>
<td>Day 14</td>
<td>0.3 (−3.7 to 6.7)</td>
<td>0 (−4.6 to 4.8)</td>
<td>0.4 (−5.4 to 4.7)</td>
</tr>
<tr>
<td>Lar relaxation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 h</td>
<td>−1.2 (−7.2 to 2.9)</td>
<td>−0.3 (−5 to 3.7)</td>
<td>−0.8 (−7.2 to 3.9)</td>
</tr>
<tr>
<td>Day 7</td>
<td>−1 (−6.7 to 4.5)</td>
<td>0 (−3.5 to 4.4)</td>
<td>−0.9 (−5.6 to 4)</td>
</tr>
<tr>
<td>Day 14</td>
<td>−0.1 (−5.8 to 5.9)</td>
<td>0 (−5.8 to 3.9)</td>
<td>−0.1 (−6.1 to 6.4)</td>
</tr>
</tbody>
</table>

A: acupuncture; M: morphine; AM: both acupuncture and morphine; Lar: line analogue rating. Kruskal–Wallis test has been used for comparisons.

Table 6
Mean (SD) change from baseline anxiety and depression score (HAD scale) at follow-up by treatment.

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm M</th>
<th>Arm AM</th>
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</thead>
<tbody>
<tr>
<td>HAD anxiety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>−0.8 (2.8)</td>
<td>−0.2 (2.9)</td>
<td>−1.1 (2.6)</td>
</tr>
<tr>
<td>Day 14</td>
<td>−0.6 (3.2)</td>
<td>−0.2 (3.1)</td>
<td>−0.9 (2.7)</td>
</tr>
<tr>
<td>p = 0.171</td>
<td></td>
<td>Interaction p = 0.895</td>
<td></td>
</tr>
<tr>
<td>HAD depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>−0.7 (2.5)</td>
<td>0.1 (2.6)</td>
<td>−1.1 (1.9)</td>
</tr>
<tr>
<td>Day 14</td>
<td>−0.8 (2.8)</td>
<td>−0.2 (2.3)</td>
<td>−0.02 (2.80)</td>
</tr>
<tr>
<td>p = 0.129</td>
<td></td>
<td>Interaction p = 0.125</td>
<td></td>
</tr>
</tbody>
</table>

A: acupuncture; M: morphine; AM: both acupuncture and morphine; SD: standard deviation; HAD: hospital anxiety and depression. Two-way analysis of variance has been used for comparisons.

Table 7
Mean (SD) change from baseline mean global health scores on EORTC QLQ at follow-up by treatment.

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm M</th>
<th>Arm AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>6.91 (25.20)</td>
<td>0.89 (13.15)</td>
<td>4.67 (17.26)</td>
</tr>
<tr>
<td>Day 14</td>
<td>7.25 (26.15)</td>
<td>−5.49 (21.46)</td>
<td>0.91 (16.69)</td>
</tr>
<tr>
<td>p = 0.009</td>
<td></td>
<td>Interaction p = 0.539</td>
<td></td>
</tr>
</tbody>
</table>

SD: standard deviation; EORTC: European Organisation for Research and Treatment of Cancer; QLQ: quality-of-life questionnaire; A: acupuncture; M: morphine; AM: both acupuncture and morphine. Two-way analysis of variance has been used for comparisons.

Forty-seven patients were randomised to a session of acupuncture (followed by acupuncture studs) or placebo acupuncture (followed by acupressure studs). Whilst the results were negative, there were study limitations with higher dyspnoea scores in the acupuncture group and the sham treatment group having one real acupuncture stud inserted.

Rescue morphine was not provided to arm A patients until 4 h and therefore would not have affected the primary end-point. Twenty-one percent of arm A patients took rescue morphine. Of these, four (36%) were non-responders at 4 h, and only one (9%) became a responder after taking morphine.

VAS dyspnoea score at 90 min has been previously reported as a reasonable end-point in a cancer population [13]. In our study, the greatest effect was seen at 4 h, with a trend seen at 30 min (Fig. 3). Although the Borg scale showed a significant difference at 30 min, no difference was seen at other time points. This may be because the Borg scale is a verbal scoring system; fail
patients may find a VAS scale easier to use. The Borg scale is more sensitive for smaller sample sizes in COPD trials [24]. In future, we recommend VAS dyspnoea between 90 min and 4 h.

Only 13% of subjects had a PS of 3. There was a higher dropout rate for PS 3 patients. Despite this, all arms had similar response rates at 4 h. PS 3 subjects had a 75% response rate in arm AM.

No significant differences were seen in lung function — morphine and acupuncture probably reduce the sensation of dyspnoea rather than any physiological action.

Morphine alone increased anxiety. Acupuncture was anxiolytic with a significant improvement in VAS relaxation, alone and in combination with morphine. The effect was evident at 90 min, maximal at 4 h but sustained to 2 weeks. There was an improvement in Lar anxiety scale in the two acupuncture-inclusive arms at 7 d. Oxytocin is released by acupuncture and is anxiolytic [25]. We postulate that massaging the studs empowered patients and may have released oxytocin. This hypothesis needs further testing.

The trial population had high levels of anxiety and depression with all patients having depression HAD of >7 and 71.5% having anxiety HAD of >7 [26]. Lung cancer patients have high rate of depression, having a negative effect on symptoms [27]. Positive findings are reported for acupuncture in the treatment of anxiety, although studies tend to only consider acute anxiety [28]. Repeat HAD at 7 and 14 d showed a similar, though smaller, trend to VAS, suggesting that HAD may not be as sensitive as VAS at an early time point. These results were similar to the pilot study previously reported [13].

In keeping with acupuncture effect, measurement of the global health domain in the EORTC QLQ showed significant improvements in the acupuncture-inclusive arms compared to arm M, with a greater than six-point change. This finding needs further exploration.

The median morphine dose was lower and fewer patients took morphine in arm A than arms M and AM. The morphine sparing effect of acupuncture has not been previously reported. No difference was seen between arm A and AM in use of the stud massage. Studs were massaged up to 32 times a day, reflecting how symptomatic patients were. Acupuncture had fewer side-effects than morphine. Therefore, acupuncture may be an alternative in those suffering opioid-related adverse effects.

5. Conclusions

Acupuncture alone or in combination with morphine is effective for the relief of dyspnoea. Acupuncture is morphine-sparing and anxiolytic with minimal toxicity in breathless patients with lung cancer.


