Clinical effectiveness and safety of acupuncture in the treatment of irradiation-induced xerostomia in patients with head and neck cancer: a systematic review

E M O’Sullivan,1 I J Higginson2

ABSTRACT

Background Irradiation-induced xerostomia seriously reduces quality of life for patients with head and neck cancer (HNC). Anecdotal evidence suggests that acupuncture may be beneficial.

Objective To systematically review evidence on clinical effectiveness and safety of acupuncture in irradiation-induced xerostomia in patients with HNC.

Methods A detailed search was performed to identify randomised controlled trials (RCTs) and systematic reviews of RCTs on acupuncture in irradiation-induced xerostomia, using AMED, BNIJA, CINAHL, Cochrane, Embase, HPSI, PsycINFO and Medline. Grey literature was explored and 11 journals hand searched. Search terms included: acupuncture, xerostomia, salivary hypofunction, hyposalivation, dry mouth, radiotherapy, irradiation, brachytherapy, external beam. Two authors independently extracted data for analysis using predefined selection criteria and quality indicators.

Results 43 of the 61 articles identified were excluded on title/abstract. 18 articles underwent full-text review; three were deemed eligible for inclusion. Two trials had moderate risk of bias; one had high risk. Two trials compared acupuncture with sham acupuncture; one control arm received ‘usual care’. Outcome measurements included salivary flow rates (SFRs) in two trials and subjective questionnaires in three. All three trials reported significant reduction in xerostomia versus baseline SFR (p<0.05); one reported greater effect in the intervention group for stimulated SFR (p<0.01). Subjective assessment reported significant differences between real acupuncture and control in two trials (p<0.02–0.05). Insufficient evidence was presented to undertake risk/benefit assessment.

Conclusions Limited evidence suggests that acupuncture is beneficial for irradiation-induced xerostomia. Although current evidence is insufficient to recommend this intervention, it is sufficient to justify further studies. Highlighted methodological limitations must be dealt with.

INTRODUCTION

Xerostomia is defined as the subjective sensation of oral dryness which is usually, but not invariably, associated with a decrease in salivary production.1 The term ‘xerostomia’ is frequently ascribed to several related conditions—namely, ‘dry mouth’, ‘salivary gland dysfunction’, ‘hyposalivation’, ‘hyposial’ and ‘salivary gland hypofunction’. While the last terms should theoretically be reserved for cases with an objective change in the quality or quantity of saliva, these terms are frequently used interchangeably.2 Xerostomia is a common complaint affecting 10–29% of the general population.3 Many cases of dry mouth are drug related, as over 400 commonly used drugs are xerogenic1,4; however, the aetiology is frequently multifactorial.5 The prevalence is higher among older patients, those with multiple comorbidities, polypharmacy, advanced disease and those who have received head and neck irradiation.6–10 Thus it is a common concern to all areas of medicine, particularly primary care.

Irradiation-induced xerostomia

Radiation-induced xerostomia is common among patients with head and neck cancer (HNC), as radiotherapy fields frequently encompass many of the major salivary glands. Destruction of highly radiosensitive salivary acini causes a quantitative and qualitative reduction in salivary flow. The degree of dysfunction is directly related to the amount of salivary gland tissue lying within the irradiation fields and total dose delivered.10 Radiation damage to salivary gland tissue is rarely reversible once the accumulated dose exceeds 24–26 Gy, with severe dysfunction occurring above 52 Gy.11,12 As patients with HNC routinely receive 60–70 Gy, many (95–100%) may have chronic xerostomia,13,14 resulting in increased susceptibility to oral infections (candidiasis, caries, periodontitis, sialadenitis, cheilitis), taste disorders, sore throat, hoarseness, dry/crusted nasal passages, sleep disruption, fatigue and social isolation.15,16,17 The impact of radiation-induced xerostomia and its complications on quality of life (QoL) is well documented; …the chronic after-effects of radiation therapy may impair QoL more severely than cancer itself.16 Although the UK cancer reform strategy has emphasised the need for rehabilitative care of cancer survivors to improve QoL,18 therapeutic options for radiation-induced xerostomia remain limited.

Diagnosis

Diagnosis is generally based on the history and clinical assessment; additional investigations may include sialography, scintigraphy, microbiology, serology and histology. Clinically, the mucosa appears dry, red, shiny and sticky, while the tongue is atrophic, dry and fissured. Saliva appears viscous, ropy, foamy or non-existent.
with reduced/absent salivary pooling. Subjective measurement tools include xerostomia inventory (XI), \( XQ \) and \( XQ-10 \). Objective measurements include sialometry (salivary flow rates (SFRs)) and the presence/absence of salivary pooling. However, SFRs vary considerably among individuals and are further influenced by multiple factors such as stress, hydration, stimulation, season, time of day, etc. Furthermore, a patient's subjective perception of dry mouth does not necessarily correlate with their objective signs of salivary gland dysfunction. This has led the Food and Drug Administration to acknowledge only subjective outcome measures for assessing benefit in patients with xerostomia.20

Therapeutic options

Conventional treatment focuses on (A) behaviour modification, fluoride supplements and xerogenic medication review; (B) salivary replacement treatment; (C) mechanical and pharmacological stimulants; (D) cytoprotectants and (E) improved radiation dosimetry. Unfortunately, salivary replacements are largely ineffective, providing short-term relief at best,6 while pharmacological stimulants may produce unpleasant adverse effects—for example, sweating, nausea, urinary frequency, cardiac arrhythmias, and are poorly tolerated or contraindicated in many patients.21 22 Concerns exist about the selectivity, safety and side effects of cytoprotectants such as amifostine, while access to advanced irradiation techniques (intensity modulated radiation therapy, three-dimensional conformal radiotherapy) is currently restricted.23

Role of acupuncture

The failure of conventional medicine to alleviate this condition has led to a resurgence of interest in the age-old practice of acupuncture.13 24 Acupuncture has gained acceptance as a valid intervention for patients with cancer who have pain and nausea; emerging reports also suggest that acupuncture may be effective in the treatment of xerostomia and may offer longlasting benefits of up to 3 years.20 Studies suggest that needling induces physiological effects, modulates neurological processes within the central nervous system, especially the spinal cord gating mechanisms, cerebral subcortical nuclei and hypothalamic-endocrine axis26; it promotes release of neuropeptides and endogenous opioids, stimulates the autonomic nervous system and increases peripheral blood flow.27 Salivary levels of vasoactive intestinal polypeptide and calcitonin gene-related peptide are also enhanced.28 29 However, the mechanism of action remains poorly understood. Furthermore, many fundamental questions remain unanswered about the relative value of the various consultation stages, optimal position/depth of needling and treatment duration/frequency. Even proponents of acupuncture admit it “has not been shown beyond doubt to be more efficacious than a placebo”.30 Up-to-date accurate information is clearly required to determine the efficacy, effectiveness and appropriateness of this intervention.

Justification for systematic review

A search of the database of abstracts of reviews of effects, Cochrane Database of Systematic Reviews (CDSR) and Scottish Intercollegiate Guidelines Network (SIGN) revealed the absence of any Cochrane review on this topic. CDSR listed just one ‘other review’ by Jedel.27 However, a review of this paper disclosed certain limitations, suggesting a comprehensive, up-to-date search examining the effectiveness and safety of acupuncture in the treatment of irradiation-induced xerostomia was justified.

METHODS: REVIEW PROTOCOL

Research question and objectives

This review aimed to answer the following research question: Is acupuncture an effective and safe treatment for radiation-induced xerostomia in patients with HNC? The primary objectives were to assess whether patients with irradiation-induced xerostomia gain:
1. any objective relief from acupuncture
2. a subjective benefit from acupuncture.

The secondary objectives were to assess whether:
1. the acupuncture treatment protocols employed in the included trials were similar
2. the frequency and nature of adverse events is acceptable.

Eligibility criteria for the review (PICOS elements)

Detailed information on the Participants, Interventions, Comparisons and Outcomes and types of Study (PICOS) to be included are provided in table 1, as advocated by the 2009 Centre for Reviews and Dissemination handbook.31 Since no clear definition of ‘placebo acupuncture’ currently exists, inactive control interventions such as sham acupuncture techniques (insertion of needles into non-acupuncture points or use of non-penetrating needles) are currently considered the most acceptable comparators for acupuncture studies.30 32 Timing of the

Table 1  Prespecified eligibility criteria

<table>
<thead>
<tr>
<th>Participants</th>
<th>Interventions</th>
<th>Comparison</th>
<th>Outcomes</th>
<th>Study types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only studies involving patients with HNC, aged ≥18 years with irradiation-induced xerostomia will be included regardless of care setting, radiation modality or dosage</td>
<td>Only studies using traditional or manual acupuncture and electro-acupuncture included. Variations in dosage, intensity, mode of delivery, personnel, timing, frequency and duration will be tolerated. ‘Non-needling’ techniques will be excluded—for example, laser acupuncture, acupressure or acupuncture-like transcutaneous nerve stimulation</td>
<td>Placebo controls are required. Sham acupuncture using inactive points, superficial needling and non-penetrating needles are deemed acceptable</td>
<td>Only studies using one or more of these tools are eligible. Objective: Salivary flow rates (resting +/or stimulated)</td>
<td>Only RCTs and systematic reviews of RCTs will be included. If no such trials identified, high-quality non-RCTs will be included in the review</td>
</tr>
</tbody>
</table>

HNC, head and neck cancer; RCT, randomised controlled trial.
outcome assessment was grouped into three prespecified intervals—‘short-term’, ‘medium-term’ and ‘long-term’. Information on nature/timing/severity of adverse events was deemed desirable but not essential.

Study design
This review was limited to randomised controlled trials (RCTs) and systematic reviews of RCTs, accepting the likely paucity of such studies as these studies represent the highest level of evidence (level 1) currently available according to the SIGN revised grading system and Cochrane Handbook. Similarly, acupuncture research methodologists consider “the highest level of evidence of effectiveness is a well-performed systematic review that considers appropriate, high-quality RCTs.” As scoping searches suggested a paucity of research in this area, the authors decided to apply a high level of sensitivity and low specificity to the search process and to include high-quality non-RCT studies (level 2+), if no RCTs could be identified.

Search strategy
A comprehensive search was undertaken, employing the following resources:

2. MESH headings and keywords included acupuncture, xerostomia, salivary hypofunction, hyposalivation, dry mouth, radiotherapy, irradiation, brachytherapy and external beam, combined using Boolean logic (AND, OR, NOT). To increase sensitivity, no restrictions were placed on language or study/trial/review type.

Applying selection/eligibility criteria to search results
Search results were merged using ReferenceManager 12 software, and duplicates/multiple reports were removed leaving 61 articles. Forty-three reports were excluded after review of the title and abstract (figure 1: PRISMA flow chart). Reasons for exclusion included inappropriate acupuncture techniques, xerostomia not a major focus, non-irradiation-induced xerostomia, study type (details available on request). Review process was undertaken by two reviewers independently, applying blinding to reduce bias.

Full texts of 18 reports were sought. The full-text reports were independently examined by both authors for compliance with eligibility criteria (table 2); 15 studies were excluded. Three RCTs were deemed suitable for inclusion. Basic study design characteristics were collected and tabulated (table 3), using a custom-designed data extraction form designed according to Cochrane review checklist 7.3a.

Critical appraisal and quality assessment
Research may vary considerably in methodological rigour and flaws in the design or conduct of a study can introduce bias, obscuring the benefit/harm of an intervention. Each study included in a review must therefore undergo a quality assessment (QA) process. The Cochrane Review Handbook (8.3.3) discourages the use of QA scales, advocating simple approaches for assessing validity that can be fully reported. The Jadad (1996) scale is explicitly discouraged as “it does not cover one of the most important potential biases in randomized trials—namely, allocation concealment.” The NHS Critical Appraisal Skills Programme (CASP) critical appraisal tool for RCTs was chosen for this review as it covers sequence generation, allocation sequence concealment, blinding, incomplete outcome data and selective outcome reporting.

RESULTS AND DATA SYNTHESIS
Data extraction sheets and CASP-QA forms were completed for each study. Interventions are assessed in table 3 using the revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) checklist. Meta-analysis was considered inappropriate for this review owing to the small number of included studies and differences in study methods. However, a brief qualitative analysis of the evidence is presented in narrative form, supplemented by tables 3 and 4.

Protocol issues
While the three trials (123 participants) included in this review were classified as ‘RCTs’, only Cho et al. provided sufficient details of the randomisation process. In a preliminary report, Pfister et al. said patients were randomised by patient or clinician preference; however, a recent report on the same study
Table 2  Characteristics of 18 for full-text review

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Title</th>
<th>Database UI</th>
<th>Eligible acupuncture technique used</th>
<th>Focus is RT-induced xerostomia</th>
<th>Study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blom et al (1992)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>The effect of acupuncture on salivary flow rates in patients with xerostomia</td>
<td>Ovid MEDLINE(R) UI – 8762876</td>
<td>Yes</td>
<td>Yes</td>
<td>Controlled clinical trial not RCT</td>
</tr>
<tr>
<td>Blom et al (1996)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Acupuncture treatment of patients with radiation induced xerostomia</td>
<td>EBSCO AN: 10326815</td>
<td>Yes</td>
<td>Yes</td>
<td>RCT</td>
</tr>
<tr>
<td>Blom et al (1999)&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Prognostic value of the pilocarpine test to identify patients who may obtain long-term relief from xerostomia by acupuncture</td>
<td>Ovid MEDLINE(R) UI – 10673783</td>
<td>Yes</td>
<td>No</td>
<td>Before/after comparative study</td>
</tr>
<tr>
<td>Blom and Lundberg (2000)&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment</td>
<td>Ovid MEDLINE(R) UI – 2000348228</td>
<td>Yes</td>
<td>No</td>
<td>Before/after comparative study</td>
</tr>
<tr>
<td>Deng et al (2008)&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Functional MRI changes and saliva production associated with acupuncture at LI2 acupuncture point: an RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>RCT</td>
</tr>
<tr>
<td>Jedel (2005)&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Acupuncture in xerostomia: a systematic review</td>
<td>CINAHL AN2009046149</td>
<td>NA</td>
<td>Yes</td>
<td>Systematic review</td>
</tr>
<tr>
<td>Johnstone et al (2002)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Acupuncture for xerostomia: clinical update</td>
<td>EMBASE UI – 2002067438</td>
<td>Yes</td>
<td>No</td>
<td>Before/after comparative study, not RCT, no control group</td>
</tr>
<tr>
<td>Johnstone et al (2001)&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Acupuncture for pilocarpine-resistant xerostomia following RT for head and neck malignancies</td>
<td>EMBASE UI – 2001188504</td>
<td>Yes</td>
<td>Yes</td>
<td>Before/after comparative study, not RCT</td>
</tr>
<tr>
<td>Meidell and Holritz Rasmussen (2009)&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Acupuncture as an optional treatment for hospice patients with xerostomia: an intervention study</td>
<td>EBSCO AN –36221591</td>
<td>Yes</td>
<td>No</td>
<td>No control</td>
</tr>
<tr>
<td>Pfister et al (2001)&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Acupuncture for pain and dysfunction after neck dissection: results of an RCT</td>
<td>Ovid MEDLINE(R) UI – 20406930</td>
<td>Yes</td>
<td>Yes as secondary outcome</td>
<td>RCT</td>
</tr>
<tr>
<td>Pinkovish (2009)&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Acupuncture and acupuncture for side effects of RT</td>
<td>EMBASEUI – 2009496876</td>
<td>No</td>
<td>No</td>
<td>Commentary on Garcia et al</td>
</tr>
<tr>
<td>Simcock et al (2009)&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Group acupuncture to relieve radiation-induced xerostomia: feasibility study</td>
<td>Ovid MEDLINE(R) UI – 19734380</td>
<td>Yes</td>
<td>Yes</td>
<td>Pilot study, not RCT, no control group, N=12</td>
</tr>
<tr>
<td>Taromina and Rooney (2006)&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Acupuncture</td>
<td>EMBASE UI 2006087992</td>
<td>NA</td>
<td>No</td>
<td>General review</td>
</tr>
<tr>
<td>Wong et al (2003)&lt;sup&gt;31&lt;/sup&gt;</td>
<td>A phase I-II study in use of acupuncture-like transcutaneous nerve stimulation (ALTENS) in the treatment of radiation-induced xerostomia in patients with HNC treated with radical RT</td>
<td>EMBASE UI – 2003348228</td>
<td>No</td>
<td>No</td>
<td>Not RCT, no control group</td>
</tr>
<tr>
<td>Wong et al (2007)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>A phase II randomised study of ALTENS for the prevention of radiation-induced xerostomia in patients receiving radical radiotherapy for HNC</td>
<td>CINAHL AN – 2009766830</td>
<td>No</td>
<td>Yes</td>
<td>Full paper requested but not accessible—does not appear to be relevant as ALTENS used</td>
</tr>
</tbody>
</table>

HNC, head and neck cancer; RCT, randomised controlled trial; RT, radiotherapy.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Participants (n)</th>
<th>Intervention and comparator interventions</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blom et al (1996)</td>
<td>Number: 41 enrolled; 38 included in analysis</td>
<td>1. Acupuncture rationale: traditional Chinese acupuncture; limited reasoning provided for treatment. Treatment partially individualised 2. Needling details: Needle insertions per case per session: not stated Points used: various points from list of 28 Depth of insertion: not stated Responses sought: needling response 0/1</td>
<td>Measured and reported Defined: SFR defined but subjective tool not defined Tools: (A) SFR: stimulated + unstimulated (B) Execution Quotient (XQ): Questionnaire subjective assessment but only 4 of the 8 questions used</td>
<td>Significant improvement in 50% of both groups. No significant difference between real and sham acupuncture (SA) groups Adverse events: brief mention of tiredness + small haematomas in a few patients but group unspecified</td>
</tr>
<tr>
<td>Cho et al (2008)</td>
<td>Number: 12 enrolled</td>
<td>1. Acupuncture rationale: manual acupuncture; little reasoning provided for treatment. Treatment variation none 2. Needling details: Needle insertions per case per session: not stated Points used: ST6, LI4, ST36, SP6 Depth of insertion: 1.5 cm Responses sought: not stated Stimulation: none Needle retention time: 20 min Needle type: Zeus Korea Acupuncture Dev Co diameter 0.20 mm, length 30 mm 3. Treatment regimen: Number of sessions: 12 Frequency: twice weekly Duration of sessions: 20 min per session 4. Other components of treatment: none stated Setting: unspecified 5. Practitioner background: unspecified 6. Control or comparator: sham acupuncture using inactive points 2 cm from active points and superficial intradermal needling with no stimulation</td>
<td>Measured, reported and defined Tools: (A) SFR: stimulated + unstimulated (B) Execution Quotient (XQ): Questionnaire subjective assessment but only 4 of the 8 questions used Scales explained Follow-up: short-term 6 weeks</td>
<td>Significant difference in SFR + XQ scores between baseline and 6 weeks in the active group, but no significant difference in scores between active and control. XQ improved by 2.33 points in RA vs 0.33 in SA group (p &lt; 0.05) Adverse events: no information provided</td>
</tr>
<tr>
<td>Study ID</td>
<td>Participants (n)</td>
<td>Intervention and comparator interventions</td>
<td>Outcomes</td>
<td>Results</td>
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<tr>
<td>Pfi ster et al (2010)</td>
<td>47</td>
<td>Acupuncture rationale: traditional Chinese acupuncture; limited reasoning provided for treatment. Partly individualised: 8–26 points</td>
<td>Measured, reported and defined with questionnaire used with standardised scoring methods.</td>
<td>Significantly greater reduction in xerostomia inventory (XI) score 52.6±21.6 compared with control or comparator: 'usual care' provided to control with no attempt made to replicate the acupuncture experience. Adverse events: no serious adverse events; 27 minor events; pain, bruising or bleeding and GI upset.</td>
</tr>
</tbody>
</table>

**Review of objectives**

**Do patients with irradiation-induced xerostomia gain any objective relief from acupuncture?**

Only two trials used objective outcome measurements: Blom et al reported an improvement of >20% in both stimulated and unstimulated SFR in the experimental group. However, the control group also showed positive changes in SFR, albeit at a lower level. Significant differences were reported between baseline levels of unstimulated saliva (p<0.05–0.01) and stimulated saliva (p<0.01) within groups but not between the experimental and control group. Similarly, Cho et al found acupuncture significantly increased unstimulated SFR compared with the baseline scores (0.04±0.06 to 0.07±0.07, p<0.05). However, flow rates also improved in the control group and no significant differences were seen between the active and control groups. As a change from baseline over time in the experimental group is not generally accepted as evidence of an effect unless the change is greater than the change in the control group, this review concludes that there is no evidence that patients with radiation-induced xerostomia derive any objective benefit from acupuncture.

**Do patients with irradiation-induced xerostomia gain any subjective benefit from acupuncture?**

All three studies undertook subjective assessment, using a variety of measurement tools. Blom et al reported that many patients in the experimental group experienced symptomatic relief (improved quality of saliva, taste, appetite, sleep and a reduction in hoarseness, nausea, pain and weight loss). However, there was no statistically significant difference in symptomatic relief between the experimental and control groups. Cho et al found that acupuncture significantly improved the XQ score by 2.33 points (11.17±4.31 vs 13.5±3.56) compared with only 0.33 in the control group (7.67±0.82 vs 7.33±1.37, p<0.05). Pfi ster et al reported a significantly greater reduction in XI scores for the acupuncture group (mean score 52.6±21.6) compared with ‘usual care’ group (61.8±18.9, p<0.02). This review concludes that there is evidence that patients with radiation-induced xerostomia derive a subjective benefit from acupuncture.

**Assessment of the uniformity of acupuncture treatment protocols employed**

This review highlighted the complete lack of uniformity or consistency seen in just three studies as the number of acupuncture points ranged from four to 29, while the number of sessions ranged from four to 24. Duration of follow-up varied from

states that random assignment was implemented via secure computerised database ensuring full allocation concealment. The review process highlighted many other concerns about the methods employed, including failure to deal with confounders, lack of information on patient allocation or stratification, significant variation in intervention technique and small case numbers. Furthermore, the lack of information for study setting, timing, recruitment process, provider’s qualifications or expertise, etc, makes it difficult to assess whether these results can be extrapolated and applied to different populations and settings.
Table 4  Quality assessment (QA) overview

<table>
<thead>
<tr>
<th>Study</th>
<th>QA summary table</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blom et al (1996)</td>
<td>Methods: RCT but no details provided about randomisation, stratification or allocation process; patients simply assigned randomly to treatment group or control. Groups relatively well balanced for gender and age (median and range similar in both groups) suggesting some stratification. Salivary flow rate (SFR) measurements were double blinded. Study quality: Selection bias: randomisation vague. Differences between groups for duration of xerostomia acknowledged. Performance bias: all reviewed at similar time intervals but no details provided on setting or provider. Detection bias: no evidence of outcome assessment bias as double-blinded, objective outcome measurement used (SFR). The subjective questionnaire, self-completed, should be free from observer bias. Attrition bias: 41 subjects were enrolled but only 38 completed the study. Four of the five lost to follow-up were from the control group. All 38 were included in the analysis, suggesting an 'intention-to-treat' approach adopted. Attrition bias should therefore be minimal. Overall assessment: This trial is of intermediate quality with moderate risk of bias.</td>
</tr>
<tr>
<td>Cho et al (2008)</td>
<td>Methods: RCT but randomisation vague as no details of stratification or allocation process. Subjects allocated into real acupuncture (RA) or sham acupuncture (SA) groups using 'block randomisation'. Blinding undertaken. Study quality: Selection bias: randomisation vague; considerable gender imbalance (10 men, 2 women) — both women in control group. No information given on mean, median and age range per group. Authors acknowledged the difference in xerostomia severity as execution quotient scores and SFRs were twice as high in RA group at the start. Median time since radiotherapy was 35.5 months in the RA group vs 6.5 months in the SA group. Performance bias: all reviewed at similar time intervals but no details provided on setting or provider. Detection bias: while single blinding employed, objective outcome measures (SFR) should be free of outcome assessment bias while subjective questionnaire, if self-completed, should be free from observer bias. Attrition bias: no attrition reported. Overall assessment: Study of intermediate quality with moderate risk of bias.</td>
</tr>
<tr>
<td>Pfister et al (2010)</td>
<td>Methods: Described as prospective ‘open-label’ RCT. Preliminary report on this study in 2008 stated patients allocated simply by patient or clinician preference but recent paper (2010) states random assignment implemented via secure computerised database ensuring full allocation concealment. Stratification details provided but unclear. Groups were relatively well balanced for age (median and range similar in both groups) but marked gender imbalance in control group acknowledged (7 women, 23 men). Xerostomia analysis stratified by four further variables but seems to include 7 cases who received no radiation, comprising 7% of the active group and 17% of the control group. Study quality: Selection bias: randomisation undertaken. Recruitment process has potential for bias as relatively small numbers enrolled over 3 years based on names chosen from database, selective referral by clinicians, self-referral. Performance bias: all reviewed at similar time intervals. Multiple acupuncturists used, range 3–20 years in experience. However, training and supervision provided to ensure uniformity of technique. Detection bias: no objective assessment undertaken. Subjective questionnaire, if self-completed, should be free of observer bias. However, the lack of sham intervention in control arm may influence participants’ responses. High risk of bias as no blinding of participants or investigators. Attrition bias: only 58 of the 70 enrolled in this study completed it. Twelve failed to complete the final follow-up but no details provided on reasons for withdrawal. Analysis adopted an ‘intention-to-treat’ approach to analysis to minimise attrition bias. Overall assessment: Trial of poor quality with high risk of bias in relation to the use of acupuncture in treatment of xerostomia. However, xerostomia was a secondary end point in this study.</td>
</tr>
</tbody>
</table>

4 weeks to 12 months. Furthermore, although acupuncture is highly technique sensitive, few details were provided about the experience, case load or qualifications of the various acupuncturists.

**Is the frequency and nature of adverse events acceptable?**

Attempts to ascertain the risk/benefit ratio for this intervention were hampered by a paucity of information, as one study (Cho et al<sup>[46]</sup>) provided no information. The other authors claimed that acupuncture is associated with minimal risk as no serious adverse events were reported; the frequency of ‘minor’ events ranged from ‘a few’ to 27. This review therefore finds that there is insufficient evidence to determine the safety of this intervention.

**DISCUSSION**

Anecdotal and clinical evidence suggest a potentially beneficial role for acupuncture in the treatment of radiation-induced xerostomia. Indeed, several high-quality phase II non-randomised and non-controlled studies have suggested that this intervention has merit. However, this systematic review indicates that there is currently insufficient ‘high-quality’ evidence to advocate the use of acupuncture as a treatment for irradiation-induced xerostomia. The lack of evidence may be due to true lack of effect or to our failure to:

1. Appreciate the multifactorial nature of xerostomia and to understand the true bio-physiological basis of acupuncture; this may result in a lack of appropriate stratification for confounding factors.
2. Establish the relative value of each component of the acupuncture consultation: discussion, listening, nurturing, needling and stimulation.
3. Provide full details on adverse events, thus hindering meaningful risk/benefit analysis.
4. Resolve protocol issues—for example, relative value of specific acupuncture points, number of points to include, optimal intervention frequency and comparability of various techniques (manual, traditional Chinese, acupuncture, TENS/ALTENS-acupuncture, electro-acupuncture), dosage (level and method of stimulation, depth of application).

**ORIGINAL PAPER**

needing). Indeed, the lack of standardisation and transparency poses a major ‘stumbling block’ in complementary and alternative medicine (CAM) research generally. This problem is difficult to resolve as no ‘gold standard’ acupuncture protocol exists for treating xerostomia.²⁰ Furthermore, the personalised nature of the treatment given to each individual is considered a crucial component of care in traditional Chinese acupuncture and CAM. Skilled practitioners may therefore consider the introduction of any single ‘gold standard’ acupuncture protocol restrictive and counterproductive.

5. Resolve the placebo controversy, which thus remains a major obstacle to future work. No agreement exists about what constitutes an acceptable comparator for acupuncture as non-needling techniques do not accurately replicate the experience while needing ‘inactive’ points appears to produce a positive physiological response. Identification of a validated, inert comparator must be considered a priority, to prevent future RCTs from being doomed to failure.

CONCLUSION

The profound impact of chronic radiation-induced xerostomia on the QoL of patients with HNC is beyond dispute. This condition is inadequately dealt with by conventional medicine, but a growing body of clinical evidence suggests that acupuncture may provide significant symptomatic relief. However, this review indicates that there is still insufficient evidence from high-quality RCTs to support acupuncture as an effective treatment for radiation-induced xerostomia.

This review also highlights many important methodological issues that must be dealt with before an effective RCT can be undertaken, particularly the need to standardise treatment and to develop a valid comparator. The introduction of additional outcome measures—for example, a diary of daily fluid intake and record of sleep disturbance, might be beneficial. The use of the revised STRICTA guidelines²⁹ for future publications is encouraged as this will facilitate review and replication. The search for an appropriate comparator can best be resolved by international collaboration and co-ordinated East–West medical research so that all can benefit from the vast body of wisdom accumulated in Eastern countries about this ancient skill.

SUMMARY POINTS

- Irradiation-induced xerostomia is debilitating and difficult to treat.
- Previous reports have suggested a therapeutic role for acupuncture.
- A systematic review of three studies found no evidence of objective benefit but suggests that acupuncture may provide significant symptomatic relief.
- Further research is warranted.

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COMPETING INTERESTS

None.

PROVENANCE AND PEER REVIEW

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16. Blom M, Davidson I, Fernberg JO, et al. Treatment of xerostomia with radiation, acupuncture, and CAM. Skilled practitioners may therefore consider an appropriate comparator to best be resolved by international collaboration and co-ordinated East–West medical research so that all can benefit from the vast body of wisdom accumulated in Eastern countries about this ancient skill.


Clinical effectiveness and safety of acupuncture in the treatment of irradiation-induced xerostomia in patients with head and neck cancer: a systematic review

E M O'Sullivan and I J Higginson

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