RTOG 0537 shows acupuncture-like ENS may provide relief for radiation-induced dry mouth

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Phase III results of Radiation Therapy Oncology Group (RTOG) 0537 indicate that acupuncture-like, transcutaneous electrical nerve stimulation (ALTENS) may be equally effective as pilocarpine, the current prescription medication in a pill, to treat radiation-induced xerostomia (dry mouth), according to a study published in the June 1, 2015 issue of the *International Journal of Radiation Oncology * Biology * Physics (Red Journal)*, the official scientific journal of the American Society for Radiation Oncology (ASTRO). RTOG 0537 is a phase II/III, multi-center, randomized trial comparing ALTENS with pilocarpine, which is the current standard of treatment for radiation-induced xerostomia.

RTOG 0537 was designed based on evidence published in 2003 (1) from a nonrandomized, phase II trial that ALTENS was a potential alternative treatment for radiation-induced xerostomia. ALTENS treats symptoms through electrodes placed on the skin at the locations of pre-selected acupuncture points. The electrodes deliver low-frequency, high-intensity pulses to stimulate acupuncture points in order to relieve the radiation-induced dry-mouth. Phase II results of RTOG 0537, published in 2012 (2), proved a positive response in patients who received ALTENS for radiation-induced xerostomia and demonstrated it was feasible to deliver ALTENS treatment in a multi-center trial.

The Phase III stage of the study accrued 148 patients from August 2010

to December 2011 at 13 cancer centers in the United States and Canada. Eligible patients had completed radiation therapy with or without chemotherapy three months to two years prior to enrolling in the study with no evidence of recurrence; reported grade 1 or higher xerostomia based on the Common Terminology Criteria for Adverse Events version 3.0; and had a Zubrod performance status of zero to two. (The Zubrod score indicates a patient's health status from zero to four, with zero indicating a patient is "fully active, able to carry on all pre-disease activities without restriction" and four indicating a patient is "completely disabled, cannot perform any self-care, and totally confined to bed or chair.") After enrollment, two patients were considered ineligible because their chemotherapy regiment or their physical examination and history were conducted outside of the maximum eight-week period before enrolling in the study.

Of the 146 patients included in the study, 73 patients were randomized to receive ALTENS, and 73 patients were randomized to receive pilocarpine. All patients began treatment within 14 days of enrolling. Patients in the ALTENS arm received two, 20-minute ALTENS sessions each week for 12 weeks (total of 24 ALTENS sessions). Patients were allowed two weeks of no treatment, and any missed sessions were rescheduled during the 12-week period; patients did not exceed three sessions per week. Patients in the pilocarpine arm received 5 mg of pilocarpine orally three times a day for 12 weeks; missed doses were not administered at a later time. Ninety-three percent (68) of patients in the ALTENS arm completed more than 85 percent of treatments, compared to 73 percent (53) of patients in the pilocarpine arm who completed more than 85 percent of the treatment.

Patients' xerostomia symptoms were assessed at baseline (before treatment) and at four, six, nine and 15 months after the patient's randomization date using the University of Michigan's Xerostomia-Related Quality of Life Scale (XeQOLS). XeQOLS is a patient-reported,

15-item scale that measures four domains: physical functioning, pain/discomfort, personal/psychologic functioning and social functioning. Patient responses to all four domains were averaged, and the total scores ranged from zero to four; an increased xerostomia burden is indicated by a higher score.

At nine months after randomization, 96 patients from both arms had completed all items to be included in the analysis. Four patients in the ALTENS arm and 11 patients in the pilocarpine arm had withdrawn from the trial. Five patients did not complete the baseline assessment prior to treatment, and 11 patients did not complete the XeQOLS prior to treatment. Six patients in the ALTENS arm and 13 in the pilocarpine arm either did not complete the XeQOLS or completed the XeQOLS outside of the designated time period.

In the 96 patients eligible for analysis, the mean baseline XeQOLS score of the ALTENS arm was slightly lower than the pilocarpine arm (1.5 compared to 1.7), which indicates a slightly higher quality of life for patients in the ALTENS arm. Baseline XeQOLS scores were subtracted from follow-up XeQOLS scores; a negative change would indicate improvement in xerostomia burden. At the nine-month follow-up (the study's primary endpoint), the median change in XeQOLS score was -0.53 for patients in the ALTENS arm and was -0.27 for patients in the pilocarpine arm. At follow-up 15 months from randomization, the median change in XeQOLS score was -0.60 for patients in the ALTENS arm and was -0.47 for patients in the pilocarpine arm. The median change in XeQOLS scores consistently improved for patients in the ALTENS arm, however, none of the differences were statistically significant. The proportions of patients who had 20 percent or more improvement from their baseline XeQOLS scores were consistently higher in the ALTENS arm and the difference was significant at 15 months from randomization.

Overall results yielded one grade three adverse event (headache) in the ALTENS arm, and two grade three adverse events (dry mouth and blurred vision) in the pilocarpine arm. In the ALTENS arm, 20.9 percent (15) of patients reported nonhematologic adverse events of grade three or less. In the pilocarpine arm, 61.6 percent (45) of patients reported nonhematologic adverse events of grade three or less. At follow-up nine months from randomization, there was no significant difference in the highest grade of adverse events related to treatment between the two arms of patients.

"Radiation-induced xerostomia is a challenging side-effect to treat because it makes it difficult and sometime painful for patients to swallow food, thereby affecting their nutrition and physical well-being. Oral pilocarpine and similar medications are not well tolerated by patients due to various side effects including sweating, diarrhea, frequent urination and dizziness. Multiple previous studies using needle acupuncture supported the potential for acupuncture approaches in treating xerostomia symptoms, so RTOG 0537 was developed to specifically explore those findings," said Raimond K.W. Wong, MBBS, the study's lead author, and a radiation oncologist and associate professor in the Department of Oncology at McMaster University in Hamilton, Ontario. "These phase III results of RTOG 0537 indicate that ALTENS, a needle-less acupuncture approach, could provide an alternative treatment option that has fewer side effects and, in turn, helps improve quality of life for patients with radiation-induced xerostomia. Some patients in the ALTENS group demonstrated lasting response and indicated the possibility to induce salivary gland tissue regeneration. Randomized, controlled, placebo trials are necessary to confirm ALTENS' treatment efficacy for painful, radiation-induced dry mouth, a debilitating condition for many patients."

More information: 1. Wong RK, Jones GW, Sagar SM, et al. A Phase I-II study in the use of acupuncture-like transcutaneous nerve stimulation

in the treatment of radiation-induced xerostomia in head-and-neck cancer patients treated with radical radiotherapy. *Int J Radiat Oncol Biol Phys*. 2003; 57: 472-480.

2. Wong RK, James JL, Sagar S, et al. Phase 2 results from radiation therapy oncology group study 0537: A phase 2/3 study comparing acupuncture-like transcutaneous electrical nerve stimulation versus pilocarpine in treating early radiation-induced xerostomia. *Cancer*. 2012; 118: 4244-4252.

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