Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 2, pp. 472–480, 2003

0360-3016/03/$–see front matter

ELSEVIER

doi:10.1016/S0360-3016(03)00572-8

CLINICAL INVESTIGATION **Head and Neck**

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

RAIMOND K. W. WONG, M.B.B.S.,*† GLENN W. JONES, M.D.,*† STEPHEN M. SAGAR, M.D.,*† ANGELICA-FARGAS BABJAK, M.D.,‡ AND TIM WHELAN, M.D.*†

Departments of *Medicine, Division of Radiation Oncology and ‡Anaesthesia, McMaster University, Hamilton, ON, Canada; †Department of Radiation Oncology, Hamilton Regional Cancer Centre, Hamilton, ON, Canada

Purpose: **Recent studies have suggested that acupuncture may improve radiation-induced xerostomia with an increase in the median salivary flow rate and sustained symptom relief. An acupuncture-like transcutaneous nerve stimulation method (Codetron) without invasive needles was developed to mimic acupuncture treatment. This Phase I–II study examined the effectiveness of Codetron in treating radiation-induced xerostomia.**

Methods and Materials: **Patients with symptomatic xerostomia after radical radiotherapy for head-and-neck cancer but with evidence of residual salivary function were recruited into the study. Two 6-week courses of Codetron treatment of acupuncture points preselected according to traditional Chinese medicine principles were given with a 2-week break between each course. Basal and citric acid-primed whole saliva production were measured at baseline and up to 1 year after treatment completion. Xerostomia symptoms were assessed by a five-item xerostomia symptom questionnaire with a visual analog scale and quality of life was evaluated using the Head and Neck Radiotherapy Questionnaire.**

Results: **We enrolled 46 patients in the study. All patients had received radiotherapy doses of ≥50 Gy to bilateral head-and-neck fields, including the parotid glands. Of the 46 patients, 37 completed the follow-up assessments at 3 and 6 months after treatment completion. No Codetron treatment-related complications occurred. Improvement in xerostomia symptoms was noted, with a mean increase in the visual analog scale score of 86 ($p < 0.0005$) and 77 ($p < 0.0001$) at 3 and 6 months after treatment completion, respectively. For all patients, the increase in the mean basal and citric acid-primed whole saliva production at 3 and 6 months after treatment completion was also statistically significant ($p < 0.001$ and $p < 0.0001$, respectively). No statistically significant change in the quality-of-life evaluation compared with baseline was observed.**

Conclusion: **The results suggest that Codetron treatment improves whole saliva production and related symptoms in patients with radiation-induced xerostomia. The treatment effects were sustained for at least 6 months after Codetron treatment completion. A prospective randomized Phase III trial with appropriate controls is being planned.** **© 2003 Elsevier Inc.**

Codetron, Acupuncture, Radiotherapy, Xerostomia, Clinical trials.

INTRODUCTION

Xerostomia or dry mouth is a very common complication in patients treated with radical radiotherapy (RT) for head-and-neck cancer and represents a significant source of morbidity for the patient population. The condition is caused by radiation damage to the salivary glands. It has been shown that the reduction in salivary flow depends on the radiation dose delivered and the volume of salivary glands irradiated. Even a low dose of radiation can cause a change in the quantity and quality of saliva, and up to 100% of patients who undergo RT for head-and-neck cancer develop some degree of xerostomia (1, 2). The symptoms of radiation-induced xerostomia are often permanent and lead to diffi-

Reprint requests to: Raimond K. W. Wong, M.B.B.S., Department of Radiation Oncology, Hamilton Regional Cancer Centre, 699 Concession St., Hamilton, ON L8V 2C5 Canada. Tel: 905-387-9495; Fax: 905-575-6326; E-mail: raimond.wong@hrcc.on.ca

Presented at the American Society for Therapeutic Radiology and Oncology Meeting, San Francisco, November 2001 and the Canadian Association of Radiation Oncologists Annual Meeting, Toronto, October 2002.

Supported by the Hamilton Health Sciences Corporation Foundation; the equipment was supported by EHM Rehabilitation Technologies Inc.

Acknowledgments—The authors thank Pat Lee, the study clinical trial nurse, for her great effort and the Head and Neck Cancer Disease Site Team at the Hamilton Regional Cancer Centre for entering patients into the study. The authors also thank Dr. Ranjan Sur for his help in reviewing this manuscript.

Received Jan 29, 2003, and in revised form Apr 28, 2003. Accepted for publication May 1, 2003.

culty in mastication, swallowing, and speaking (2). Other consequences include stomatitis, taste dysfunction, and increased susceptibility to dental caries (3).

Treatments with saliva substitutes and stimulation of salivary flow by either mechanical or pharmacologic methods provide some symptomatic relief but no long-lasting results when active treatment is stopped (3). Oral pilocarpine hydrochloride treatment has been the most extensively studied and is commercially available for treating xerostomia. Despite a modest effectiveness with overall improvement in symptoms, adverse cholinergic effects, such as sweating, nausea, rhinitis, and chills, limit pilocarpine use. In several studies, 15–25% of patients had to withdraw from treatment because of intolerable side effects (4–6).

Recently, acupuncture treatment in patients with xerostomia has been demonstrated to be effective and associated with long-lasting results (7). In patients with radiation-induced xerostomia, acupuncture treatment has been shown to improve salivary flow rates and, qualitatively, led to a reduction in xerostomia-related symptoms with minimal side effects (8–10). Moreover, long-term improvement in the salivary flow rate for up to 6 months after the first course of treatment, and up to 3 years with additional acupuncture treatments, has also been shown in a recent study (11).

Although quite promising, the reluctance of patients to undergo "needle therapy" (12) and the requirement for expertise in performing the acupuncture treatment may make this treatment modality difficult to offer to patients in most conventional clinics. To overcome this shortfall, non-invasive transcutaneous electrical nerve stimulation (TENS) of acupuncture points has been used to replace the needles. TENS has been shown to give comparable results to acupuncture treatment for musculoskeletal pain disorders (13, 14). Recently, a newer approach to transcutaneous nerve stimulation, using Codetron machines, has been developed to deliver stronger and less habituating stimulation to the nerves using a lower frequency than conventional TENS devices. This approach allows stimulation of the Aδ muscle afferent neurons, resulting in an ache similar to the sensation that actual acupuncture treatment creates when correctly done, the so-called De Qi sensation (15, 16). In a randomized study, it was shown that Codetron provided comparable or better results than electroacupuncture in the treatment of chronic musculoskeletal pain (17). Like conventional TENS therapy, only minimal side effects occur with the use of Codetron, consisting of mild ache and skin irritation at site of stimulation (18, 19).

Given the evidence that TENS-like devices are effective in treating disorders responsive to acupuncture, we hypothesized that radiation-induced xerostomia may also be responsive to Codetron therapy. This is the report of our prospective Phase I-II randomized trial conducted to evaluate the usefulness of Codetron treatment of radiation-induced xerostomia.

METHODS AND MATERIALS

We enrolled 46 patients who had been treated for head-and-neck cancer with radical RT who had symptoms of xerostomia. No evidence of active cancer was found after 4 months of follow-up in all patients. All patients had had both parotid glands irradiated but had some residual salivary function, as evidenced by the presence of oral moisture on physical examination. Patients who were taking medications that may induce xerostomia, who had unstable cardiac disease, or who had a pacemaker *in situ* were excluded from the study. Patients who were taking pilocarpine for ophthalmic or nonophthalmic indications were also excluded. Patients for whom oral pilocarpine treatment of radiation-induced xerostomia had failed and who had stopped taking the medication for more than 1 month were included.

After informed consent, the study patients were centrally randomized into three groups (A, B, and C). Each of these three groups was treated with a predetermined set of acupuncture points for Codetron stimulation. This randomization progress was performed with the aim of determining the optimal combination of acupuncture points for stimulation. The sets of acupuncture points (named according to the World Health Organization Standard Acupuncture Nomenclature [20]) were as follows:

Group A: Sp6, St36, LI4 (active electrodes) and CV24 (indifferent electrode)
Group B: Sp6, St36, P6 (active electrodes) and CV24 (indifferent electrode)
Group C: Sp6, St5 and 6, P6 (active electrodes) and CV24 (indifferent electrode)

The acupuncture points used in this study were selected on the basis of the meridian principles described in traditional Chinese medicine (21). The combinations vary in the relative contribution of local and distal points, as well as potential sympathetic and parasympathetic stimulation (21, 22). These acupuncture points have also been used in previous xerostomia studies (7, 8).

Codetron treatment was given twice weekly for 6 weeks. Nonpolarizing, balanced, biphasic, square electrical pulses of 250-ms duration were delivered in trains with a repetition rate of 4 Hz (recurrence frequency, code III on the Codetron machine). The intensity of stimulation of each acupuncture point was adjusted to produce a deep, strong, with or without mild aching, sensation at the attachment point of the electrodes. Each acupuncture point was randomly stimulated for 10 s each time. Each session of Codetron treatment lasted for a total of 20 min. This was followed by a 2-week break and then another 6-week course of treatment was repeated.

The quantification of response was performed using a five-item xerostomia symptom questionnaire with a visual analog scale (VAS) used in previous trials (5, 6) (Fig. 1). The VAS for each item was set up with the most negative response (i.e., the worst symptom or zero score) as the left anchor and the most positive response (i.e., the absence of symptoms or score of 100) as the right anchor; thus, the

INSTRUCTIONS: Below are several questions which will help describe the dryness in your mouth and how that dryness interferes with aspects of your daily life. Please make one vertical mark across the line to show your condition.

E.g.: Very dry _____/_____ Not dry

1. During the past week, overall, your mouth or tongue was:

   very dry _____ *not dry*

2. In general, during the past week, the feeling of your mouth and tongue was:

   extremely _____ *comfortable*
   uncomfortable

3. During the past week, overall, due to the dryness of your mouth and tongue, how difficult was it to speak without drinking liquids:

   very _____ *easy*
   difficult

4. During the past week, overall, due to the dryness of your mouth and tongue, how difficult was it to chew and swallow food:

   very _____ *easy*
   difficult

5. The overall condition of your xerostomia (dry mouth) is:

   very _____ *very*
   uncomfortable *comfortable*

Fig. 1. VAS of xerostomia symptoms.

higher the score, the better the symptom. The *total* VAS scores for the five items combined could range from 0 to 500. Patients were asked to mark on the scale their response relative to the two extremes. Standardized assessments of whole saliva production (WSP) for 5 min for basal production and citric acid-primed production were conducted. WSP was measured by expectoration weight, assuming 1 g of saliva produced equaled 1 mL of saliva. Patients were asked to refrain from eating, drinking, and smoking at least 1 h before each measurement. For the basal WSP measurement, patients were asked to expectorate continuously into a preweighed dry plastic container during a 5-min period without swallowing. The collected saliva with the plastic container was weighed (total weight) immediately after each collection. The total weight minus the weight of the container was taken as the weight or volume of whole saliva collected. For the citric acid-primed WSP measurement, the above procedure was performed after the patient swished with 1 mL of citric acid for 1 min (5, 6). The quality of life was evaluated using the Head and Neck Radiotherapy Questionnaire (23). All assessments were performed at baseline and 6, 8, and 12 weeks after treatment began and at 3, 6, and 12 months after treatment completion.

Repeated measures analysis of variance was conducted to compare the results after treatment during follow-up with those at baseline.

Ethics approval

The Research Ethics Board of the Henderson Hospital, Hamilton Health Sciences Corporation, approved this study.

Table 1. Patient profiles

Factor	Group A	Group B	Group C
n	13	10	14
Age (y)	62.5 (49–85)	59.3 (45–77)	56.6 (30–77)
Male (*n*)	10	7	11
Female (*n*)	3	3	3
Present/past smoker (*n*)	2/7	2/5	2/8
Alcohol use (*n*)	7	6	7
Ethnic origin (n)			
White	13	8	14
Native American		2	
Education ≥high school (*n*)	12	8	12
Employed (*n*)	10	10	8

Numbers in parentheses are the range.

RESULTS

Of the 46 patients enrolled in the study, 9 patients did not complete it because of reasons unrelated to the treatment. One patient had tumor recurrence, one had hemorrhage from his prosthesis, one developed severe back pain, three had unexpected heart events, and three could not come to be treated two times weekly because of other personal commitments. The remaining 37 patients (Group A, $n = 13$; Group B, $n = 10$; Group C, $n = 14$) had all completed the follow-up assessment at 6 months after treatment completion. Patient characteristics and their disease and treatment profiles are listed in Tables 1 and 2.The mean patient age was 59.2 years (range 30–85). The average duration of xerostomia symptoms for the study patients ranged from 5 to 88 months (mean 27). All patients had received RT doses of ≥50 Gy to bilateral head-and-neck fields, including the parotid glands.

The mean total xerostomia symptom VAS score for all patients increased from 144 (standard deviation [SD] 71) at baseline to 230 (SD 107) at 3 months and 221 (SD 87) at 6 months after completing Codetron treatment. *t* tests for the differences (mean increase in total VAS score of +86 [SD 124] and +77 [SD 104] at 3 and 6 months of follow-up, respectively) were statistically significant ($p < 0.0005$ and $p < 0.0001$, respectively), indicating significant improvement in xerostomia symptoms. Patients reported improvement in tongue dryness, speech, swallowing, and overall comfort of the mouth (Fig. 2).

For all patients, the mean pretreatment 5-min basal and citric acid-primed WSPs was 0.26 mL (SD 0.28, range 0–1.29) and 1.07 mL (SD 0.78, range 0.09–3.49), respectively. At 3 months, the mean 5-min basal and citric acid-primed WSPs had increased by 0.1–0.36 mL (SD 0.39, range 0–1.49) and 0.26–1.33 mL (SD 0.81, range 1.1–3.41), respectively. At 6 months of follow-up, the mean 5-min basal and citric acid-primed WSPs had increased further to 0.37 mL (SD 0.35, range 0–1.44) and 1.61 mL (SD 1.07, range 0.30–5.07), respectively (Fig. 3). The mean

Table 2. Patient disease and treatments profiles

Factor	Group A	Group B	Group C
Stage			
TxN0-2	2	1	2
T1N0-2	6	1	3
T2N0-2	4	2	2
T3N0-2	1	6	3
T4N0-2	0	0	4
Bilateral parotid RT			
Total	13	9	10
Subtotal	0	1	4
Average total dose (Gy)/fx	6550/32	6600/32	6282/31
Average field size (cm^2)	165	177	181
Average duration of xerostomia (mo)	24 (7–88)	31 (5–68)	26 (7–74)
Radiation energy/type	6-MV photons	6-MV photons	6-MV photons

Abbreviation: RT = radiotherapy.
Numbers in parentheses are the range.

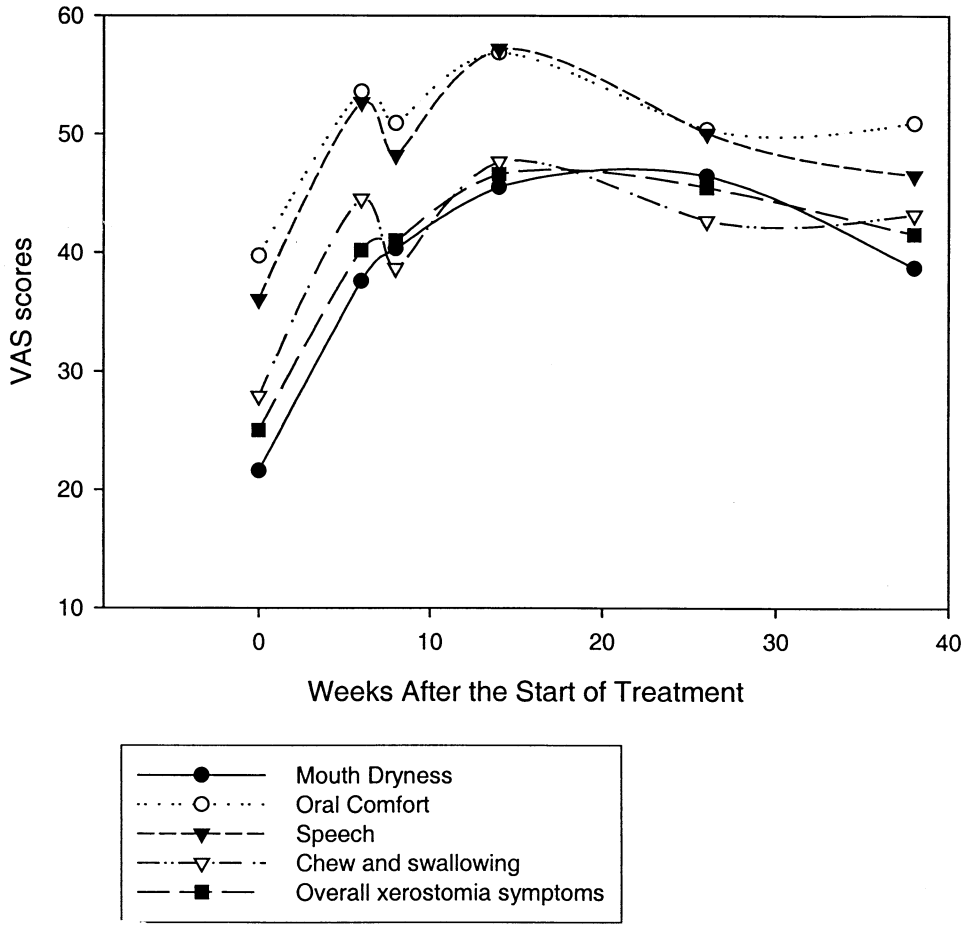

Fig. 2. Mean VAS scores of xerostomia symptoms of all patients.

increases in both basal and citric acid-primed WSPs at 3 and 6 months of follow-up were statistically significant compared with the pretreatment levels ($p < 0.001$ and $p < 0.0001$, respectively) using repeated measures analysis of variance. The mean increases remained statistically significant after covariate adjustments for concurrent tobacco and alcohol use and intervals between the last fraction of radiation and the start of Codetron treatment. The increases in WSPs were sustained for 6 months after Codetron treatment. The increase in citric acid-primed WSP was significantly better than the increase in basal WSP at 6 months of follow-up (analysis of variance, $p < 0.05$).

No statistically significant differences were found in the increases in WSP or improvements in xerostomia symptoms among groups A, B, and C at 3 and 6 months of follow-up (Fig. 4). However, a trend was noted that patients in Group A demonstrated the greatest improvement in their mean total VAS scores in all xerostomia symptoms.

No overall statistically significant difference ($p > 0.05$) was noted in most of the Head and Neck Radiotherapy Questionnaire–based quality-of-life questions at 6 months of follow-up compared with baseline for all patients. However, statistically significant improvements were reported in taste ($p < 0.004$) and consistency (less thick) for both saliva ($p < 0.0001$) and oral mucous ($p < 0.04$).

No adverse effects were caused by the Codetron treatment. All patients stated that they could operate the machines and administer their own treatments in our study survey.

DISCUSSION

In clinical studies, acupuncture treatment has been suggested to be able to relieve xerostomia symptoms and improve salivary production (7–10). The results of our study suggest that Codetron may be useful in improving symptoms related to radiation-induced xerostomia and are similar to the results obtained in studies using actual acupuncture techniques.

The possible underlying mechanism is not clear. It has been proposed that acupuncture treatment may specifically stimulate the autonomic nervous system through selected afferent neurones, causing increased activity of the parasympathetic nervous system, which enhances the release of specific neuropeptides. The neuropeptides may have a number of trophic effects that include an increase in the local

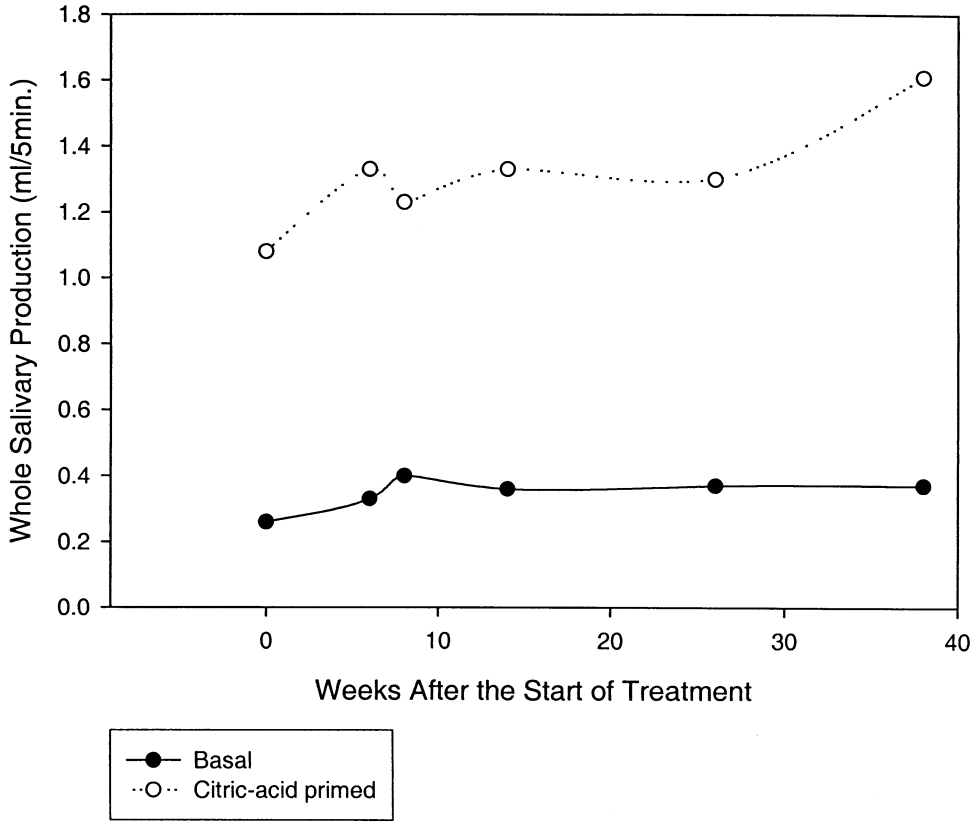

Fig. 3. Mean WSP of all 37 patients.

blood flow of the salivary glands, causing an upward regulation in the metabolism of salivary gland cells that results in an increase in salivary production and, possibly, regeneration of tissue (24–29). Another possible mechanism may involve the stimulation of minor salivary glands present in nonirradiated buccal mucosa, leading to increased salivary production and improved mucosal moisture.

The use of the transcutaneous nerve stimulator as an alternative to actual acupuncture treatment has been studied. Unlike conventional TENS, which typically uses high-frequency, low-intensity stimulation, acupuncture-like TENS (ALTENS) uses a high-intensity, low-frequency electrical stimulus that preferentially stimulates the Aδ nerve fibers that are stimulated by actual acupuncture treatment with the typical "De Qi" response (15). In studies of chronic pain conditions, ALTENS was demonstrated to provide better pain relief than conventional TENS (30). With the additional property of random stimulation, Codetron can prevent habituation of the brain to stimulation and may potentially improve the results of ALTENS therapy (16).

In our study, the choice of acupuncture points for ALTENS stimulation was largely empiric. These points were selected by two of us who were certified in medical acupuncture using the anatomic and classic traditional Chinese medicine approaches. All the points used in the study have either been described in acupuncture texts to have an effect on xerostomia conditions or been observed to have influences on the autonomic nervous systems (21, 22). The design of the combinations was based on a local and distal point approach commonly used in acupuncture practice. CV24 was selected to be the point for the indifferent electrode because the point has been used in most conditions of xerostomia from various causes. These points have also been used in the aforementioned studies of acupuncture treatment of xerostomia (7, 8).

The treatment schedule was modeled on the classic approach in treating chronic conditions, with a protracted course involving two to three acupuncture treatments weekly for a few weeks followed by a short break period, and another few weeks of active treatment.

A reduction in salivary production with associated xerostomia symptoms typically occurs during RT that involves both parotid glands (1). In a prospective study that evaluated the change in salivary production during and after RT for various head-and-neck cancers, all 14 patients who had both parotid glands irradiated were found to have a marked reduction in salivary production during the first week of treatment. A dose-dependent recovery of the salivary secretion rate was also observed. Patients whose parotid glands received $<$4500 cGy showed a mean recovery of 70% of initial salivary secretion rate at 18 months after RT completion. A mean recovery of 60% of the initial salivary secretion rate was seen in the 3 patients who received 4700–5200 cGy; only a 20% recovery rate was seen for those who received $>$6500 cGy (2). However, no correlation was found in patients' reported dryness with the sali-

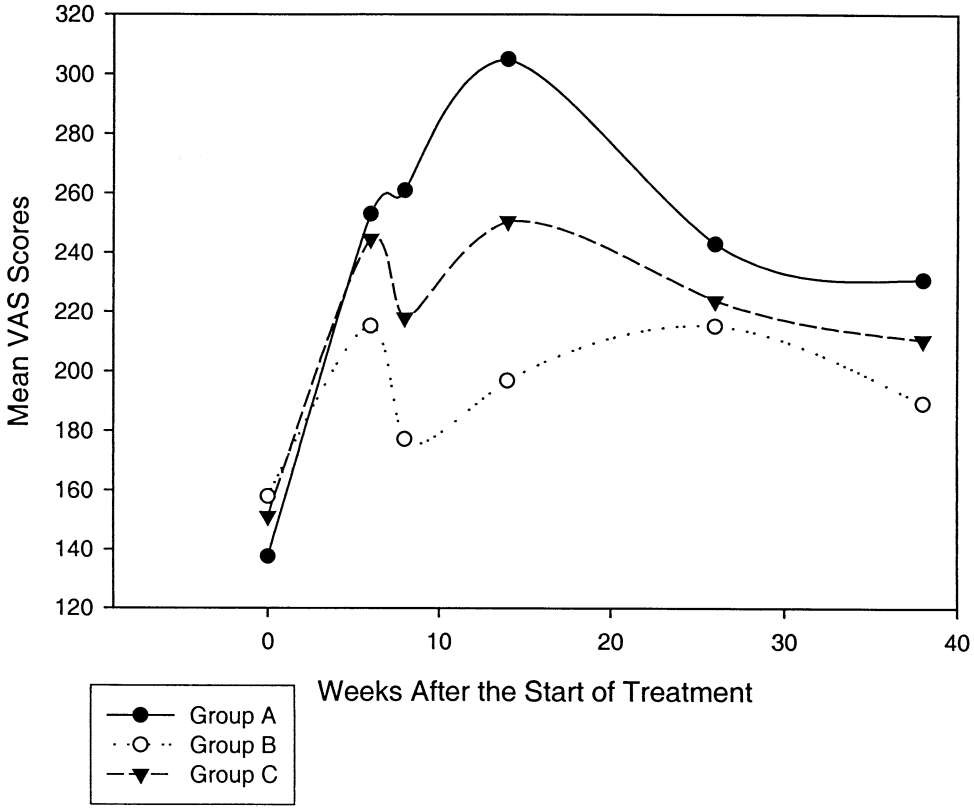

Fig. 4. Mean total VAS scores of xerostomia symptoms for Groups A, B, and C.

vary secretion rate, and two-thirds of patients continued to have a dry mouth at 18 months after RT. In our study, all patients received a dose of ≥5000 cGy to both parotid glands, and the duration of xerostomia symptoms ranged from 5 to 88 months (mean 27). Only 6 patients had an interval of <10 months (but >5 months) between the last date of RT and the first day of Codetron therapy. The observed improvements in whole salivary flow production were thus not likely to have the result of a recovery process.

The observed early response in xerostomia symptoms after the first half of Codetron treatment with a subsequent slight decline in improvement may signify a psychological reaction of well-being that might have occurred in some patients, because they had been offered a possible useful intervention that might help their debilitating symptoms. However, the sustained response in xerostomia symptoms, despite no active intervention, for at least 6 months after completion of Codetron treatment is not likely to be a result of a psychological reaction. This improvement in symptoms may be explained by the small, but definite, sustained increase in citric acid-primed WSP after Codetron treatment. The basal WSP was also mildly improved after Codetron treatment at 6 months. The significance of this is still uncertain. In other clinical studies, no strict correlation was found between patient reports of xerostomia symptoms and saliva production (2, 5). It was found that electrical stimulation of the parasympathetic nerve to the parotid and submandibular glands in rats causes a mitogenic response, as indicated by an increase in tritiated thymidine uptake of the glands (31). The question of whether these improvements in citric acid-primed and basal WSP are due to salivary gland tissue regeneration remains to be answered by future studies.

In our study, we failed to demonstrate any significant improvement in the overall quality-of-life score for the patients we studied, despite significant improvement in xerostomia symptoms. Although a number of studies have documented the impact of cancer- and treatment-related complications on the quality of life in head-and-neck cancer patients (32–34), no study has yet shown that an improvement in established treatment-related complications will enhance quality of life in head-and-neck cancer patients. In a study comparing health-related quality of life in long-term head-and-neck cancer survivors with that of the general population, no clear correlation was found between reported functional problems and general function and mental health, reflected as no statistically significant change in quality-of-life scores at 3 years after diagnosis (35).

The finding of a sustained response in our study is also compatible with the results of a recent long-term follow-up study of patients with xerostomia treated with acupuncture. In that study, significant increases in salivary flow rates at 6 months of follow-up ($p < 0.01$) were found after 24 acupuncture treatments. Patients who received additional acupuncture treatment in their follow-up period had consis-

tently greater salivary flow rates at 3 years of follow-up (36).

In our study, we attempted to determine the best combination of acupuncture points for Codetron treatment of radiation-induced xerostomia by randomizing patients into three groups treated with three slightly different combinations of acupuncture points. We found no statistically significant differences in the increases in WSP or improvements in xerostomia symptoms among the three groups at 3 and 6 months of follow-up. This implied that the use of any of the three combinations of acupuncture points used in this study for Codetron treatment of radiation-induced xerostomia can be similarly effective. However, in our study, a trend was noted that the patients randomized to Group A had the greatest improvement in xerostomia symptoms. This suggests that the combination of acupuncture points used in Group A be examined further in future trials. In classic traditional Chinese medicine, single or multiple acupuncture points have been found useful in treating xerostomia from a variety of etiologies. Within this paradigm of practice, patients with identical symptoms may have different individual constitutions requiring treatment with different combinations of acupuncture points. This individualized approach, based on patients' constitutional patterns, has been found to produce better treatment results (21). A comparison of acupuncture point combinations, without defining the constitutional subgroups, may be less likely to demonstrate a statistically significant difference. The generalization of patients with radiation-induced xerostomia to be treated with a single combination of acupuncture points may limit treatment efficacy. However, in a clinical trial setting, generalization is obviously more practical even if it introduces simplistic standardization.

No adverse effects related to Codetron treatment occurred, and this was expected on the basis of the experience from studies using similar ALTENS and conventional TENS therapies (19, 37). The medical conditions that occurred in the 6 patients who discontinued treatment were probably not caused by the treatment. That three patients did not complete the treatment because they could not feasibly come to the cancer center to be treated is clearly a practical problem for any form of treatment that requires frequent visits. Treatment compliance has been shown to be a significant issue in disease management. Codetron, however, can be self-administered by most patients. This will likely improve compliance. In our study, all patients found it easy to deliver the treatment with the machine and expressed willingness to treat themselves at home. The noninvasiveness and ease of Codetron treatment also make it easier to implement it into practice in most oncology or nononcology settings. By following a simple protocol consisting of an acupuncture point combination, accurate treatment can be delivered without special acupuncture training on the part of certified health providers such as physicians, nurses, or physiotherapists. However, the legal prescription and use of Codetron and other similar TENS machines is still governed by local legislation.

Given the positive results obtained in this Phase I-II study, it is appropriate to examine the usefulness of Codetron for the treatment of radiation-induced xerostomia in a Phase III randomized controlled trial. Placebo treatment can be available with the use of "sham" machines that have all the identical electronic features of active machines but give no or a small amount of electrical stimulation. A Phase III trial of Codetron treatment of radiation-induced xerostomia is being organized at the Hamilton Regional Cancer Centre with a planned total accrual of 100 patients.

The role of pilocarpine in preventing radiation-induced xerostomia has not been encouraging. In a well-designed placebo-controlled trial of oral pilocarpine given concurrently and after RT, no statistically significant difference was found between the control and experimental arms. The prophylactic use of a radioprotector, amifostine, has also been evaluated. In a Phase III study, the concurrent use of amifostine during RT was shown to induce a statistically significant reduction in radiation-induced xerostomia (38). However, the relatively high side-effect profile, the high cost, and the necessity of i.v. administration before each RT session will likely continue to limit its widespread clinical use. Given the positive result of our current study, we have recently started a funded Phase II study of the concurrent use of Codetron treatment during RT in the prevention of radiation-induced xerostomia at the Hamilton Regional Cancer Centre.

REFERENCES

1. Dreizen S, Brown LR, Handler S, *et al.* Radiation-induced xerostomia in cancer patients. *Cancer* 1976;38:273–278.
2. Franzen L, Funegard U, Ericson T, *et al.* Parotid gland function during and following radiotherapy of malignancies in the head and neck: A consecutive study of salivary flow and patient discomfort [Abstract]. *Eur J Cancer* 1992;28:457–462.
3. Greenspan D. Xerostomia: Diagnosis and management. *Oncology (Huntingt)* 1996;10(Suppl. 3):7–11.
4. Warde P, O'Sullivan B, Aslandis J, *et al.* A phase III placebo controlled trial of oral pilocarpine in patients undergoing radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys* 2002;54:9–13.
5. Johnson JT, Ferretti GA, Nethery WJ, *et al.* Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. *N Engl J Med* 1993;329:390–395.
6. LeVeque FG, Montgomery M, Potter D, *et al.* A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. *J Clin Oncol* 1993;11:1124–1131.
7. Blom M, Dawidson I, Angmar-Mansson B. The effect of acupuncture on salivary flow rates in patients with xerostomia. *Oral Surg Oral Med Oral Pathol* 1992;73:293–298.
8. Blom M, Dawidson I, Fernberg JO, *et al.* Acupuncture treatment of patients with radiation-induced xerostomia. *Eur J Cancer B Oral Oncol* 1996;32B:182–190.

9. Johnstone PA, Niemtzow RC, Riffenburgh RH. Acupuncture for xerostomia: Clinical update. *Cancer* 2002;94:1151–1156.
10. Johnstone PA, Peng YP, May BC, *et al.* Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys* 2001;50:353–357.
11. Blom M, Lundeberg T. Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment. *Oral Dis* 2000;6:15–24.
12. Hamilton JG. Needle phobia: A neglected diagnosis. *J Fam Pract* 1995;41:169–175.
13. Fox EJ, Melzack R. Transcutaneous electrical stimulation and acupuncture: Comparison of treatment for low-back pain. *Pain* 1976;2:141–148.
14. Laitinen J. Acupuncture and transcutaneous electric stimulation in the treatment of chronic sacrolumbalgia and ischialgia. *Am J Chin Med* 1976;4:169–175.
15. Eriksson M, Sjolund B. Acupuncture-like electroanalgesia in TNS resistant chronic pain. In: Zotterman Y, editor. Sensory functions of the skin. Oxford: Pergamon Press; 1976. p. 575–581.
16. Pomeranz B, Niznik G. Codetron, a new electrotherapy device overcomes the habituation problems of conventional TENS devices. *Am J Electromed* 1987;2:22–26.
17. Cheng RSS, Pomeranz B. Electrotherapy of chronic musculoskeletal pain: Comparison of electroacupuncture and acupuncture-like transcutaneous electrical nerve stimulation. *Clin J Pain* 1987;2:143–149.
18. Codetron operational manual. North York, ON: EHM Rehabilitation Technologies; 1990.
19. Corraza M, Maranini C, Bacilieri S, *et al.* Accelerated allergic contact dermatitis to a transcutaneous electrical nerve stimulation device. *Dermatology* 1999;199:281.
20. Standard acupuncture nomenclature. Manila: WHO Regional Office for the Western Pacific; 1993.
21. Cheng X. Chinese acupuncture and moxibustion, 1st ed. Beijing: Foreign Languages Press; 1987.
22. Wong JY. A manual of neuro-anatomical acupuncture, volume I: Musculo-skeletal disorders, 1st ed. Toronto, ON: Toronto Pain & Stress Clinic; 1999.
23. Browman GP, Levine MN, Hodson DI, *et al.* The Head and Neck Radiotherapy Questionnaire: A morbidity/quality-of-life instrument for clinical trials of radiation therapy in locally advanced head and neck cancer. *J Clin Oncol* 1993;11:863–872.
24. Blom M, Lundeberg T, Dawidson I, *et al.* Effects on local blood flux of acupuncture stimulation used to treat xerostomia in patients suffering from Sjögren's syndrome. *J Oral Rehabil* 1993;20:541–548.
25. Dawidson I, Angmar-Mansson B, Blom M, *et al.* The influence of sensory stimulation (acupuncture) on the release of neuropeptides in the saliva of healthy subjects. *Life Sci* 1998; 63:659–674.
26. Dawidson I, Angmar-Mansson B, Blom M, *et al.* Sensory stimulation (acupuncture) increases the release of vasoactive intestinal polypeptide in the saliva of xerostomia sufferers. *Neuropeptides* 1998;32:543–548.
27. Andersson S. The functional background in acupuncture effects. *Scand J Rehabil Med* 1993;29:31–60.
28. Nishijo K, Mori H, Yosikawa K, *et al.* Decreased heart rate by acupuncture stimulation in humans via facilitation of cardiac vagal activity and suppression of cardiac sympathetic nerve. *Neurosci Lett* 1997;227:165–168.
29. Haker E, Egekvist H, Bjerring P. Effect of sensory stimulation (acupuncture) on sympathetic and parasympathetic activities in healthy subjects. *J Auton Nerv Syst* 2000;79:52–59.
30. Gadsby JG, Flowerdew MW. Transcutaneous electrical nerve stimulation and acupuncture-like transcutaneous electrical nerve stimulation for chronic low back pain. Cochrane Database System Review 2000;2:CD000210.
31. Schneyer CA, Humphreys-Beher MG, Hall HD, *et al.* Mitogenic activity of rat salivary glands after electrical stimulation of parasympathetic nerves. *Am J Physiol* 1993;264:935–938.
32. Kwok HC, Morton RP, Chaplin JM, *et al.* Quality of life after parotid and temporal bone surgery for cancer. *Laryngoscope* 2002;112:820–833.
33. Jensen AB, Hansen O, Jorgensen K, *et al.* Influence of late side-effects upon daily life after radiotherapy for laryngeal and pharyngeal cancer. *Acta Oncol* 1994;33:487–491.
34. Epstein JB, Emerton S, Kolbinson DA, *et al.* Quality of life and oral function following radiotherapy for head and neck cancer. *Head Neck* 1999;21:1–11.
35. Hammerlid E, Taft C. Health-related quality of life in long-term head and neck cancer survivors: A comparison with general population norms. *Br J Cancer* 2001;84:149–156.
36. Blom M, Lundeberg T. Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment. *Oral Dis* 2000;6:15–24.
37. Johnson MI, Ashton CH, Thompson JW. Long term use of transcutaneous electrical nerve stimulation at Newcastle Pain Relief Clinic. *J R Soc Med* 1992;85:267–268.
38. Brizel DM, Wasserman TH, Henke M, *et al.* Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol* 2000;18:3339–3345.