Salivary stimulation with vitamin C at any time after ^{131}I administration has a minimal effect on salivary ^{131}I absorption

Liu B, Kuang A, Huang R, Zhao Z, Zeng Y, Wang J, Tian R. Influence of vitamin C on salivary absorbed dose of ^{131}I in thyroid cancer patients: a prospective, randomized, single-blind, controlled trial. J Nucl Med 2010. doi:10.2967/jnumed.109.071449

SUMMARY

BACKGROUND

Radioiodine (^{131}I) used in the treatment of thyroid cancer is taken up by a variety of tissues other than the thyroid, including the salivary glands, with sodium iodine symporters. As a result, ^{131}I exerts a toxic effect on the salivary glands, which are highly sensitive to β-radiation from ^{131}I. Because of this, the combination of radiation sialadenitis and xerostomia is one of the most common complications of ^{131}I therapy, which occurs even with relatively small amounts of therapeutic ^{131}I. There is uncertainty regarding how this complication can be ameliorated. The purpose of this study was to test the use vitamin C as a sour stimulant to decrease the effect of salivary ^{131}I absorption.

METHODS

This is a prospective randomized, single-blind, controlled study of patients referred to the West China Hospital Department of Nuclear Medicine for thyroid remnant ablation. Patients had stage pT1–T_3,N0–N1,M0 tumors (by tumor–node–metastasis classification) and were at least 18 years of age and had thyroidectomy for papillary or follicular carcinoma prior to being prepared for remnant ablation by thyroid hormone withdrawal. Excluded from the study were patients who had distant metastases, a history of salivary-gland disorders, collagen-tissue disease, diabetes mellitus, previous ^{131}I therapy or external radiation to the head or neck, or difficulty drinking a large amount of water.

After achieving hypothyroidism, patients were divided into four groups, A, B, C and D, all of which were treated with 3.7 GBq (100 mCi) of ^{131}I 4 to 6 weeks after thyroidectomy, including a 2-week low-iodine diet, without preceding diagnostic whole-body scanning. Patients were put on levothyroxine therapy after salivary dosimetry measurements were performed.

Six days after being treated with ^{131}I, patients were instructed to stop taking lemon candy, gum, or other sialogogues, and anticholinergic or antidepressant medications were temporarily discontinued before the study patients in all four groups began sucking on lozenges of 100 mg of vitamin C at 1, 5, 13, and 24 hours in the groups A, B, C, and D, respectively (Figure 1). Patients were treated with 10 mg of prednisone every 8 hours after ingesting at least 3000 ml of nondairy liquids.

The amount of absorbed ^{131}I was estimated using high-energy collimators that provided counts of salivary-gland uptake of ^{131}I after the detectors were positioned to cover an area from the brain to the thyroid from 1 to 48 hours after ^{131}I ingestion. The residence time of ^{131}I in salivary glands was calculated, and the salivary gland size was measured by computed tomography.

RESULTS

Patient Demographics (Figure 2)

A total of 80 patients were recruited from October 2006 through December 2008. Eight were excluded from the study, 5 did not complete salivary dosimetry measurements (2 from group A and 3 from group D), and the others had lung metastases identified on the posttherapy scans. A total of 73 patients were thus eligible for the analysis of salivary dosimetry. The main characteristics of the four study groups, including age, sex, histologic features, and thyrotropin (TSH) levels, were comparable (Figure 2).

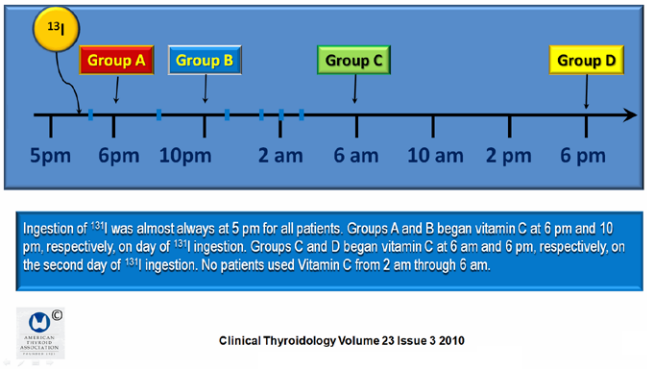

Figure 1. This figure shows the timing of vitamin C stimulation. This figure is adapted from Figure 1 by Liu et al.

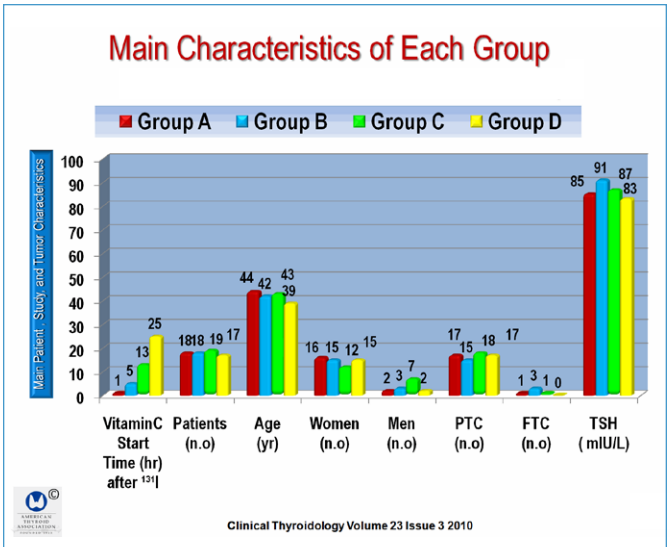

Figure 2. This figure shows the main patient and tumor characteristics of the four study groups. There are no statistically significant differences in the variables among the four study groups FTC = follicular thyroid carcinoma; PTC = papillary thyroid carcinoma; TSH = thyrotropin.

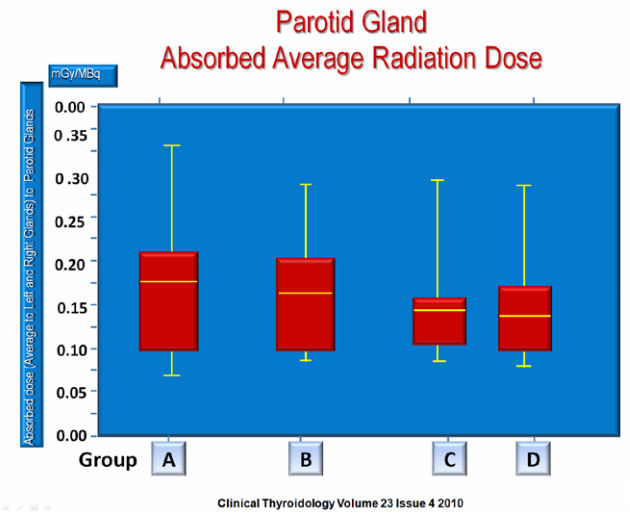

Figure 3. This figure shows box plots of absorbed ^{131}I dose to parotid and submandibular salivary glands in the four treatment groups. Error bars are 10th and 90th percentiles, and the box itself is the boundary of 25th and 75th percentiles. Solid lines indicate the medians. This figure and Figure 4 are adapted from Figure 3 of Liu et.al.

Salivary Absorbed Dose of ^{131}I to Parotid and Submandibular Glands in All Four Groups (Figure 3)

The dose of ^{131}I absorbed by the patient's single parotid gland in groups A, B, C, and D were 18±0.11, 0.16±0.07, 0.16±0.09, and 16±0.12 mGy/MBq (0.1 rad/37 mCi), respectively (P = 0.37). For the single submandibular gland, the values of the four groups were 0.19±0.05, 0.17±0.05, 0.18±0.07, and 0.17±0.06 mGy/MBq, respectively (P = 0.28) (Figure 3).

Salivary Absorbed ^{131}I Dose during the First 24 Hours (Figures 4 and 5)

The cumulative salivary ^{131}I activities arising from the first 24 hours after ^{131}I ingestion accounted for 86.08±.89% of the total cumulative ^{131}I activities, which ranged from 75 to 98% (Figure 4). There was no significant difference in the salivary absorbed dose among the four groups during the first 24 hours after ^{131}I administration (Figure 5).

Conclusion

Salivary stimulation with vitamin C at any time after ^{131}I administration had only a limited effect on salivary ^{131}I absorption in patients with thyroid cancer treated with ^{131}I for remnant ablation.

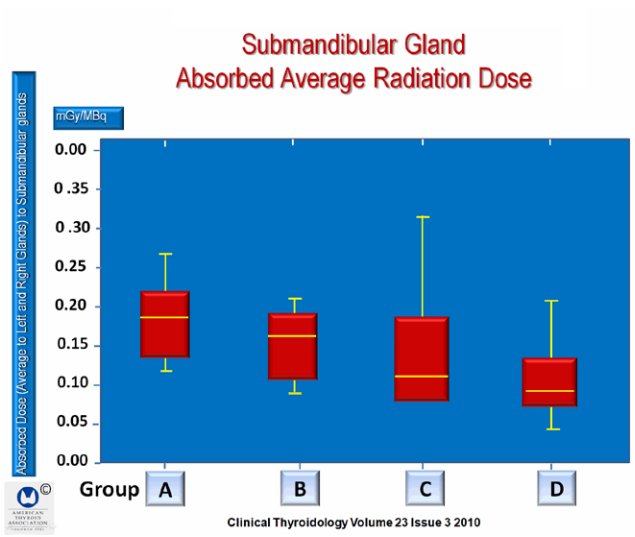

Figure 4. See Figure 3 legend.

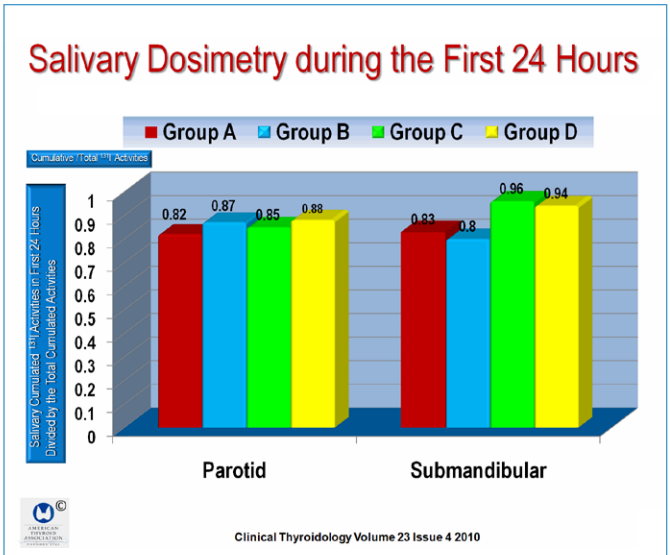

Figure 5. This figure shows the salivary dosimetry during the first 24 hours after ^{131}I therapy (cumulative/total ^{131}I activities).

COMMENTARY

This study was based on the assumption that ^{131}I uptake by salivary glands would not plateau until 24 hours after the administration of ^{131}I, similar to the uptake by thyroid tissue, and that an early start of a sour stimulation of the salivary gland in the form of vitamin C would further deliver ^{131}I by increasing blood flow to the salivary glands. There are many recognized risks of ^{131}I therapy, including hematologic malignancy and damage to other nontarget tissues. Kloos summarized this group of problems in an editorial entitled "Protecting Thyroid Cancer Patients from Untoward Effects of Radioactive Iodine Treatment" (1). In that editorial, he pointed out that the American Thyroid Association guidelines recommend the lowest activity possible for remnant ablation, especially in patients with low-risk tumors. Still, even relatively small amounts of ^{131}I, in the range of 50 mCi, may produce salivary damage (2). Several strategies have been suggested to decrease the risk of salivary damage by ^{131}I therapy.

One strategy is to use amifostine to protect normal tissue against the harmful effects of ^{131}I. In a double-blind, placebo-controlled study, Bohuslavizki et.al (3) found that amifostine protected salivary glands against ^{131}I damage, thus concluding that the drug could protect patients from salivary-gland damage induced by high-dose ^{131}I treatment. Although others have confirmed this observation (4), a randomized trial by Kim et al. (5) found a minimal effect of amifostine on ^{131}I treatment. In addition, concern has been raised that this drug might also reduce the therapeutic effect of ^{131}I.

For decades, physicians advised patients to suck lemon candy to decrease the amount of radiation to the salivary glands. In the first study to question this advice, Nakada et al. (6) performed a prospective study of 116 patients who were instructed to suck one or two lemon candies every 2 to 3 hours during the day for 5 days starting within 1 hour after ^{131}I therapy (group A), and 139 others were given the same instructions, except that they were told to wait until 24 hours after ^{131}I therapy to begin using lemon candies (group B). During a 24-month period, patients were studied using interviews and questionnaires, which found that acute sialadenitis, taste dysfunction, dry mouth, and xerostomia were reported by patients who sucked lemon candies within an hour after ^{131}I therapy, as compared with those in group B, who waited 24 hours before starting the therapy. The incidences of sialadenitis, hypogeusia (taste loss), and dry mouth with or without repeated sialadenitis in group A as compared with group B were 64% versus 37% ($P<0.001$), 39% versus 2% ($P<0.01$), and 23.8% versus 11% ($P<0.005$), respectively. Permanent xerostomia occurred in 14% of the patients in group A and in 6% in group B ($P<0.05$). In both groups, bilateral involvement of the parotid gland was most frequently seen and was followed by bilateral involvement of the submandibular gland in group A, the first cohort. However, patients in group B were treated more aggressively for side effects, including the use of steroids or nonsteroidal antiinflammatory drugs for sialadenitis, and a drug containing zinc acetate or vitamin B12 for taste dysfunction. Moreover, 52% of group A and 81% of group B received such treatment. Whether this more aggressive treatment altered the outcome of group B is unknown. Nonetheless, the study findings raised serious questions about this practice.

The study by Liu et al. is the first prospective, randomized, controlled dosimetry-based trial to explore the effect of sour stimulation on the salivary glands. They also investigated the effect of the timing of salivary-gland stimulation to detect the effect of sour stimulation on the absorption of ^{131}I by salivary glands. Liu et al. also point out that similar studies should be performed on patients prepared with recombinant human TSH for remnant ablation. Their results confirm those reported by Nakada et al. and Liu et al. also suggest that in view of the high incidence of salivary-gland injury and the wide availability of sour stimulation, future controlled studies are needed to determine not only whether sour stimulation is necessary and when it should be started, but also how the dose and frequency of the stimulation should be titrated.

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