Assessment of Salivary and Lacrimal Gland Dysfunction after Radioiodine Therapy Using 99mTc-Pertechnetate Scintigraphy

AHMED A. KANDEEL, M.D.*; MAHASSEN A. ABOU-GABAL, M.D.* and TAMER A. GHEITA**
The Departments of Nuclear Medicine (NEMROCK)* and Rheumatology**, Faculty of Medicine, Cairo University

Abstract

Background: Iodine-131 (I-131) is an effective treatment for differentiated thyroid carcinomas (DTC) after surgery. Salivary and lacrimal gland dysfunction has been described in patients receiving high doses of I-131 due to radiation damage to salivary and lacrimal glands.

Objective: This prospective study was conducted to determine the short term effect of oral I-131 therapy administered to thyroid cancer patients on the function of salivary gland by 99mTc-pertechnetate scintigraphy with semiquantitative analysis and assessment of lacrimal gland affection.

Methods: Twenty patients with post-surgical DTC (mean age, 45.6±9.7 y) were referred for I-131 therapy (mean dose 196±108 mCi). All patients had no symptoms or signs or drug history of Sicca syndrome. Before and 8-12 months after I-131 therapy, salivary gland function was estimated by sequential salivary gland scintigraphy after an intravenous injection of 185 MBq (5 mCi) 99mTc-pertechnetate with lemon stimulation at 15th min post-injection. Regions of interest (ROIs) were drawn over the four parotid and submandibular glands. Time-activity curves were generated and semiquantitative functional parameters were calculated for each gland to obtain the time at maximum count (Tmax). Clearance fraction (CF) was also calculated. Mean values of the bilateral glands were used for data analysis. Lacrimal gland function was carried out by Schirmer’s test done before and after I-131 therapy; wetting of 5mm or less was considered abnormal.

Results: Tmax and CF of parotid and submandibular glands were normal in all patients with no clinical symptoms of xerostomia at base line study. On follow-up, 7 patients reported variable severity of xerostomia. However, 12 patients showed deterioration of their salivary indices with significant difference in the Tmax and CF values between 2 studies (p 0.03, 0.01 for parotid and 0.02, 0.02 for submandibular, respectively). There was a significant positive correlation between the given I-131 dose and Tmax values (r 0.66p 0.002 for parotid and r 0.71p 0.001 for submandibular). There was a significant negative correlation between the given I-131 dose and CF values (r-0.48 p 0.03 for parotid and r-0.49 p 0.03 for submandibular). Abnormal Schirmer’s test was documented in 5 patients; yet, non-significant (p=0.41).

Conclusion: The semiquantitative analysis method including the Tmax and clearance fraction parameters would enable objective assessment of salivary gland function and provide a reproducible means for moderate term follow-up after radioiodine therapy especially those who received total doses more than 150mCi and should be closely monitored for their salivary and lacrimal function after radioiodine therapy.

Key Words: 1-131 therapy — Cancer thyroid — 99mTc-pertechnetate scintigraphy — Salivary gland dysfunction — Lacrimal gland dysfunction.

Introduction

THE use of radioiodine (I-131) therapy for the ablation of residual thyroid after surgery has become established in the management of differentiated thyroid cancer [11].

1-131 targets the thyroid gland, where it is absorbed and concentrated as part of the normal metabolic activity of thyroid cells. 1-131 plays an effective role in the treatment of papillary and follicular thyroid carcinomas because the radioactivity destroys both normal and malignant thyroid cells [2-4].

Serious acute complications are extremely rare during treatment and severe complications are uncommon [5-7]. Unfortunately, 1-131 secondarily targets the salivary glands by a carrier-mediated mechanism [8], where it is extracted from the vascular stream, concentrated and secreted into the saliva, which can cause radiation damage to these glands. Some authors reported that the concentration of 1-131 in the secreted saliva is 50 to 100 times of that found in serum [5-9].

Thus, a significant number of patients complaining of symptoms such as dryness of mouth, salivary swelling, pain in the parotid region, altered taste, and difficulty in swallowing have been described [10,11]. The symptomatology is in direct
Aim of the work:

This prospective study was conducted to determine the moderate term effect (8-12 months) of oral 1-131 therapy administered to cancer thyroid patients on the function of salivary gland using 99mTc-pertechnetate scintigraphy with semiquantitative analysis and to assess the effect on lacrimal gland function.

Material and Methods

This prospective study was conducted in Nuclear Medicine unit, Saudi-German Hospital in Yemen during the period from May 2007 to February 2009. Twenty patients with post-surgical differentiated thyroid cancer (3 men, 17 women; mean age, 45.6±9.7y; age range, 31-65y) who were referred 6-8 weeks after thyroidecomy for 131 therapy to ablate the remnant thyroid tissue or to treat metastatic tumor had received single or multiple doses of oral radioiodine-131 (mean 1-131 dose 196±108mCi; dose range 80-400mCi). A low-iodine diet was started 10 days before 131 therapy and thyroid hormone replacement was withdrawn 3-4 weeks before 131 therapy. All patients were in the hypothyroid state prior to oral 1-131 administration with their mean serum TSH level done 2-3 days before therapy was 31.2±4.911IU/ml (reference normal range was 0.4-4.20U/till). Seventeen patients had papillary carcinoma and three had follicular carcinoma. All patients were treated with L-thyroxin after therapy and none had hypothyroidism that might influence salivary gland function. All patients underwent subjective clinical evaluation to check for salivary and lacrimal gland dysfunction before and after radioiodine treatment by means of a detailed questionnaire covering the symptoms of dry mouth (dryness, dental deterioration, gingivitis, infections, parotitis, lack of taste, and difficulty in swallowing dry foods) and symptoms of dry eyes (dryness, photosensitivity, sticking, burning, heaviness, redness, and infection of the eyes) or wet eyes (epiphora). On history taking and clinical examination, there were no symptoms or signs of dryness in other mucous membranes (vaginal, nasal, etc); a detailed drug history was also obtained to exclude the presence of sicca symptoms [24]. According to revised version of classification criteria for Sjogren’s syndrome [28], patients with a previous history of salivary gland disorders, diabetes, collagen tissue disease, sarcoidosis, pre-existing lymphoma, use of anticholinergic drugs or previous 1-131 therapy or external irradiation to the neck were excluded from the study. Consents were obtained from all patients at the start of the study.
Salivary gland scintigraphy:

Imaging Technique:

Salivary gland function was estimated by sequential salivary gland scintigraphy while the patients fasted for 2h before the study and they were placed in the supine position on a couch of a dual-head gamma camera (Siemens e-cam) equipped with a low-energy, high-resolution collimator with the field of view included the head and the cervical area. After an intravenous injection of 185 MBq (5 mCi) 99mTc-pertechnetate, dynamic anterior acquisition was acquired in a 128 x 128 matrix, 1 frame per 30 seconds for 30min set at 140 KeV and 15% window with x1.85 zoom. At 15th min after injection, Salivary gland secretion was stimulated with a 2mL freshly squeezed lemon juice (without dilution) administered orally using a straw without moving, while imaging was continued. Patients were also instructed to minimize swallowing during imaging. During imaging, the study was reviewed to check for patient motion and for suitability for further analysis.

Semiquantitative analysis:

By means of e-soft software, rectangular-shaped regions of interest (ROIs) were drawn on the dynamic images of the parotid glands (right and left) and submandibular glands (right and left). Time-activity curves were generated for each region. Semiquantitative functional parameters were calculated for each salivary gland to obtain time at maximum count (Tmax), maximum counts at Tmax, and minimum count post lemon stimulation. Clearance fraction (CF) was then calculated using the equation (maximum (at Tmax)) counts minus minimum (post-stimulus) counts divide by maximum counts (at Tmax) (multiplied by 100). The mean values of the right and left glands were used for data analysis.

Lacrimal gland function was measured by Schirmer’s test performed before and after I-131 therapy during the follow-up in the same day of doing the salivary scan using standardized sterile 5 X 35mm Schirmer’s test strips that were placed, without local anesthesia, at the junction of the middle and temporal thirds of the lower lid of the right orbit. After 5 min, the strips were removed and evaluated by measuring the length of the moistened area using the millimeter scale imprinted on the strips. Wetting of the paper after 5 minutes was considered normal when 15mm. Dryness was considered mild, moderate and severe when the wetting of the paper was 10-14mm, 6-9mm and 5mm respectively [26].

Statistical analysis:

Statistical Package for Social Science (SPSS) program version 15 was used for analysis of data. Data was summarized as mean±SD. Mann Whitney test was used for comparing and analysis of 2 quantitative data. Pearson's correlation was used for detection of the relation between 2 variables. p-value was considered significant if <0.05*.

Results

At baseline study before radioiodine therapy the studied twenty patients had no clinical symptoms of dry mouth or dry eye. Salivary scintigraphy, time activity curves pattern and semiquantitative parameters showed no abnormality.

Salivary gland scintigraphy with calculation of Tmax and Clearance fraction (CF) of parotid and submandibular glands are carried out in this study for simplicity.

In the follow-up study (8-12 months) after last I-131 dose, 7/20 patients (35%) gave history of variable severity of salivary dysfunction with the most common symptom was dry mouth. However, 12/20 patients (60%) showed deterioration of their salivary indices. There was a statistically significant difference on comparing the semiquantitative salivary parameters before and after iodine therapy in the studied patients (Table 1).

Table (1): Comparison of the semiquantitative salivary parameters in thyroid cancer patients before and after iodine therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before I-131 therapy</th>
<th>After I-131 therapy</th>
<th>Significance p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.-20 patients</td>
<td>No.-19 patients</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>Mean±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax Parotid (min)</td>
<td>12.3±0.6</td>
<td>14.4±3.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Tmax SM (min)</td>
<td>11.9±1.2</td>
<td>13.4±2.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Parotid Clearance (%)</td>
<td>69.2±2.9</td>
<td>59.5±13.4</td>
<td>0.01</td>
</tr>
<tr>
<td>SM Clearance (%)</td>
<td>64.9±3.9</td>
<td>58±12.1</td>
<td>0.02</td>
</tr>
</tbody>
</table>

SM – Submandibular.

Two patients claimed severe xerostomia on follow-up, first patient received total I-131 dose of 320 mCi and the second received 350mCi. Tmax and CF of the parotid of the first (Fig. 1) and submandibular of the second could not be estimated.

It was observed that 10/12 patients with deteriorated salivary parameters had received total doses 150mCi (mean 280±92.9) with significant difference of salivary parameters when compared
with the remaining 10 patients who received doses <150mCi (mean 112±18.7) (p=0.04, 0.01 for Tmax; p=0.04, 0.02 for CF in the parotid and submandibular gland respectively).

No statistically significant sex and age differences were found in patients receiving above and below 150mCi.

Considering salivary parameters in the follow-up study, the parotid gland was affected more often (8 patients) than the submandibular gland (4 patients). Four patients showed involvement of all 4 major glands.

Concerning correlation studies, a reliance on total dose of radioiodine was significant for deterioration of the salivary parameters on the follow-up study as observed in (Fig. 2).

All patients had no symptoms of dry eye at baseline study with normal Schirmer's test. Abnormal Schirmer's test was documented in 5 patients (2 severe, 1 moderate and 2 mild). Yet, non-significant difference was elicited when compared with baseline test (p=0.41). Schirmer's test had non significant negative correlation with I-131 dose (r-0.35, p 0.13). The five patients with xerophthalmia also reported xerostomia.

In two patients (45 and 50 years old females with papillary thyroid carcinoma received total doses of 250 and 200mCi, respectively), their baseline salivary scintigraphy and semiquantitative parameters showed no abnormality without any symptoms of eye dryness and normal Schirmer's test. On follow-up after 8 and 10 months respectively, they claimed symptoms of severe xerostomia with significant deterioration of the salivary parameters on scintigraphy and severe xerophthalmia (Schirmer's test was 1 and 2mm respectively).

A female patient, 60 years old had metastatic follicular thyroid carcinoma to bone received total I-131 dose of 400mCi. Three months after the last dose, she complained of mild symptoms of dry mouth and progressive left epiphora despite taking eye therapy in the form of warm compresses, ophthalmic antibiotics, ophthalmic glucocorticoids, artificial tears and ointment, nasal glucocorticoids and eye drops for allergy. Lacrimal gland scintigraphy was performed to her on follow-up and the diagnosis of nasolacrimal duct (NLD) obstruction in the left eye was established (Fig. 3). The patient was sent later for ophthalmic intervention.

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**Fig. (1):** ROIs and actual time-activity curves of parotid glands (upper row) and submandibular glands (lower row), of a 54-yr-old woman in follow-up study 10 months after total I-131 dose of 320mCi with lemon stimulation at 15m min post-injection. Parotid gland curves show obstructive pattern. Submandibular curves show moderate and mild clearance of radioactivity in the right and left glands respectively.
Fig. (2): Correlation between 1-131 dose and semiquantitative salivary indices.

Fig. (3): Static and Dynamic lacrimal gland scintigraphy in a female patient 10 months after receiving total 1-131 dose of 400 mCi showing normal RT eye and obstructed LT eye drainage systems even after massage (NLS = Nasolacrimal sac, NLD = Nasolacrimal duct).

Discussion

Radioiodine (I-131) secondarily targets the salivary glands causing radiation damage to these glands making a significant number of patients complain of symptoms such as dryness of mouth, salivary swelling, pain in the parotid region, altered taste and difficulty in swallowing. In addition, long-term effects of high-dose radioiodine therapy on tear secretion including ocular dryness and in some cases nasolacrimal duct (NLD) obstruction have been also described.

In this study, a semiquantitative method for 99mTc-pertechnetate salivary scintigraphy analysis was used to assess the function of the parotid and submandibular glands. Semiquantitation was performed using a standard 30min dynamic imaging protocol with salivary stimulation by lemon administration as a sialogogue in the middle of the dynamic study. Time at maximum count (Tmax) and clearance fraction (CF) parameters were only calculated for simplicity providing information that could be useful to assess the moderate term effects of radioiodine therapy on the salivary glands. Schirmer's test was also performed to evaluate the possible lacrimal gland dysfunction in cancer thyroid patients after 1-131 therapy.

In the current study, salivary scintigraphy accurately showed deterioration of the semiquantitative parameters in 12/20 (60%) patients despite
only 7 of them (35%) gave history of variable severity of salivary dysfunction. Our findings are in keeping with the data of Solans et al., who reported that abnormal objective test results were more frequent than subjective symptoms when the salivary glands were evaluated [14]. Similarly, Malpani et al., observed that nearly 70% of their asymptomatic patients had demonstrable salivary dysfunction [101].

Salivary gland dysfunction has been reported in patients undergoing low and high-dose radioiodine therapy [5-7,10,11]. This may be attributed to the fact that I-131 is concentrating in the ductal cells of the salivary glands exposing them to a radiation absorbed dose of 7-15Gy [8]. Moreover, radiation is thought to induce changes in saliva composition (increased amylase and activated kallikrein) causing an obstructive process leading to reduced salivary flow and function [3,4,27].

The incidence of severe xerostomia was greater with increasing doses of radioiodine Na I-131 doses >11.1GBq (300mCi) [14]. A significant activity-related functional impairment of 10%-90% after application of 0.4-24 GBq of Na I-131 has been also reported [28]. Other reports mentioned that severe salivary gland parenchymal destruction has been documented among patients who received large doses of I-131 [5,7,10,11]. This is in accordance with our results where salivary gland dysfunction and deteriorated parameters were significantly confirmed in patients receiving total doses of I-131 >150mCi whether administered as a single high dose or as multiple doses.

Although all salivary glands are involved in the transport of I-131 into the saliva, the parotid glands have proven to be more susceptible to the development of radiation sialadenitis than are the submandibular glands [4,12,13]. The serous cells of the parotid glands have a greater ability to trap iodide than do the mucous cells of the submandibular or sublingual salivary gland complex [4,29-31]. Parotid gland secretion is usually reduced by about 40% after doses of 270mCi of I-131 [32] and by 50-60% in those who receive 500mCi of I-131 [33,34], and it approaches 100% in those who receive one curie of I-131 or more [38]. This can explain the finding in the current study that the parotid gland was affected more often (8 patients) than the submandibular gland (4 patients). In addition, time activity curves showed obstructive pattern in parotids of one patient who received total I-131 dose of 320mCi and submandibular glands of the another patient who received 350mCi. The most common symptom of theses patients was oral dryness. This obstructive pattern can be clarified by the hypothesis that radiation damage causes a glandular inflammatory infiltrate and concomitant swelling, which can lead to an increase in periductal pressure and subsequent ductal constriction [12,13,15].

Glandular injury is asymmetric and any combination of unilateral or bilateral parotid gland and/or submandibular gland involvement may develop. Generally, injury to the submandibular salivary glands becomes more apparent when large or multiple doses of radioactive iodine are administered. Furthermore, because the effects of the irradiation are asymmetric, some salivary glands can remain clinically unaffected and continue to produce normal salivary volumes [15].

With regard to assessment of dry eyes, Schirmer’s test; which measures the volume of tears produced in 5 min under basal conditions; has been shown to have high sensitivity and specificity in the hospital environment [36]. Zettinig et al., found that Schirmer’s tear test was definitely abnormal (<5mm/5min) in 40% of their studied patients after I-131 therapy [23]. Similarly, in the current study Abnormal Schirmer’s test was documented in 5/20 patients (25%) with variable severity depending on the dose given. These five patients with documented xerophthalmia had also xerostomia and impaired salivary parameters in accordance with the finding of Solans et al. [14].

I-131 is excreted in tears and is actively accumulated in the nasolacrimal duct (NLD) with a 3.4% incidence of documented nasolacrimal drainage obstruction and an overall 4.6% incidence of documented or suspected obstruction [37]. Obstruction of the lacrimal drainage system could occur after high-dose radioiodine therapy. A causal relationship between I-131 administration and NLD obstruction is strongly suspected [38]. This relationship supports our observation of 60 year-old woman who received a total dose of 400 mCi and complained of progressive left epiphora started 3 months after the last dose and NLD obstruction was confirmed by Lacrimal gland scintigraphy. Patients reporting epiphora should be evaluated promptly by an oculoplastic surgeon.

Twenty-four hours after ingestion, I-131 uptake by iodine-avid tissues reaches a plateau and the majority of radioactivity is excreted into the urine. Subsequent sucking of lemon candy does not further increase I-131 uptake in the salivary glands and predominantly helps wash I-131 out from the salivary glands. On the other hand, sialogogue may
inadequately stimulate saliva secretion in a subset of patients with an impaired patency of the salivary duct to enhance stasis of 1-131 in the duct [39]. Symptomatic improvement in patients with radiation-induced xerostomia has been reported after pilocarpine treatment (5-10mg orally three times a day) [40]. Moreover, significant improvement in symptoms of dry mouth and dry eyes after pilocarpine treatment has been reported in patients with Sjogren’s syndrome [41].

Silberstein concluded that the incidence of sialadenitis after 1-131 therapy was lower than had previously been reported in the literature with administration of pilocarpine if it is given with concurrent stringent application of physiologic sialogogues (candy, gum and fluids), dexamethasone, and dolasetron mesylate, a serotonin receptor antagonist [42]. Usually only increased fluid intake and lemon juice consumption is recommended for prevention of salivary gland damage [4]. However, it should be kept in mind that early use of sialogogue may enhance the salivary gland side effects of 1-131 therapy. For preventing life-long salivary gland complications of 1-131 therapy, the timing of lemon candy sucking should be carefully selected and lemon candy should be given after 24h following I-131 therapy [391].

Conclusion:

The semiquantitative analysis method including the Tmax and clearance fraction parameters would enable objective assessment of salivary function and provide a reproducible means for follow-up after radioiodine therapy especially those who received total doses more than 150mCi and should be closely monitored for their salivary and lacrimal function after radioiodine therapy.

References


