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ORIGINAL ARTICLE

Salivary evaluation in radioactive I^{131} treated patients with thyroid carcinoma

Filipe Ivan Daniel[a], Luiza Dutra Lima[b], Liliane Janete Grando[a], Renata Castro[c], Elke Annegret K. Cordeiro[d] and Claudia Regina Dos Santos[a]

[a]Department of Pathology, Health Science Center, Federal University of Santa Catarina, Florianopolis, SC, Brazil; [b]Health Science Center, Federal University of Santa Catarina, Florianopolis, SC, Brazil; [c]Department of Dentistry, Health Science Center, Federal University of Santa Catarina, Florianopolis, SC, Brazil; [d]Nuclear Medicine, Institute of Cardiology of Santa Catarina State, São José, SC, Brazil

ABSTRACT

Background and objective: radioiodine treatment (I^{131}) used to treat thyroid carcinomas produces side effects (sialadenitis, xerostomia, dysphagia and caries susceptibility) reflecting in a poor patient quality of life. This study aimed to evaluate the effect of I^{131} on salivary function and possible oral impairment.
Material and methods: Thirty-seven patients undergoing I^{131} were submitted to oral examination, answer questions regarding xerostomia/hyposalivation and collect saliva at three moments (M1: 30–45 days before I^{131}, M2: 1–2 days after I^{131} and M3: 7–10 days after treatment). Saliva was assayed for flow rate and calcium/phosphate concentrations.
Results and conclusions: significant difference in calcium/phosphate concentration was shown between M1 and M2, with evident decrease at M2. Flow rate reduced right after treatment with 41% of patients returning to previous rate at M3 (no statistical difference). A higher number of patients related xerostomia and difficulty in swallowing food at M2. The results showed that xerostomia/hyposalivation, dysphagia and calcium/phosphate concentration decrease may be considered early radioiodine side effects.

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Thyroid cancer; iodine radioisotopes; xerostomia; saliva; salivary glands

Introduction

Thyroid cancer treatment usually includes total or partial surgical removal with some patients being submitted to treatment with radioiodine (I^{131}), with the intention of destroying any remaining neoplastic cells not removed during surgery, including microscopic foci and metastasis treatment [1–5]. This procedure usually uses a 100–200 mCi I^{131} dose with the patient in total isolation for 48 h to avoid environmental and human contamination. Although positive results have been shown in reducing recurrence rates in patients with well differentiated thyroid carcinomas [3], some side effects such as speech variations, larynx oedema, dysphagia, hypogeusia, sialadenitis, xerostomia and caries susceptibility may occur [1,6–8]. I^{131} damage to salivary gland tissues present short- and long-term complications, reflecting in suffering and poor quality of life for oncologic patients [1,8,9], with long term effects persisting for as long as a year after the last iodine application [10].

Although salivary glands may be considered radioresistant due to their highly differentiated cells, when exposed to ionizing radiation the function is quickly affected [11], resulting in sialadenitis [12]. Some studies have been made in an attempt to detect possible salivary gland impairment that could interfere in daily oral function. Alexander et al. [10], when applying questionnaires in patients with total thyroidectomy submitted to up to 250 mCi radioiodine therapy, verified long-term side effects in 61.1% of patients, with 42.9% suffering from reduced salivary gland function. Newkirk et al. [13] showed that salivary gland dysfunction may affect 30% of patients that received 300 mCi I^{131} total dose and 50–60% of those that received 500 mCi. Almeida et al. [1], detected a strong association of I^{131} therapy with decreased excretion ability in the parotid glands, but with no influence of doses higher than 150 mCi in the $^{99m}TcO^{4-}$ elimination ability of salivary glands during scintigraphy. All of these alterations may cause important direct discomfort as a result of sialadenitis, or indirect effects such as chewing/swallowing disabilities, taste and pH alterations and pathogenic microbiota changes. As a result, patients with hyposalivation are susceptible to oral infections such as caries, periodontal disease, and candidiasis, contributing to quality of life impairment [13,14]. In order to detect saliva production and caries susceptibility modifications, the present study analysed salivary flow rates and calcium/phosphate concentrations in patients with thyroid cancer, before and after treatment with I^{131}.

Materials and methods

Subjects

The present study was approved by the Ethics Committee in Human Research (approval number 146/2011) and included

CONTACT Filipe Ivan Danie filipe.daniel@ufsc.br, filipedaniel06@gmail.com Federal University of Santa Catarina, Department of Pathology, Reitor João David Ferreira Lima Campus, 88040-900, Florianópolis, SC, Brazil

37 thyroid cancer patients that underwent radioactive I^{131} treatment at the Nuclear Medicine Service of Santa Catarina Cardiology Institute from 2012 June to 2014 February. All subjects signed an informed consent before participating in the study. Patients previously submitted to head and neck radiotherapy/I^{131}-therapy, chemotherapy or with salivary gland diseases (including Sjögren's Syndrome) were excluded.

The patients were submitted to an oral examination and answered questions regarding symptoms associated with xerostomia/hyposalivation, and saliva was collected at three different moments (M1: 30–45 days before I^{131} therapy; M2: 1–2 day(s) after I^{131} therapy, when patients left the hospital; and M3: 7–10 days after I^{131} therapy, during the control scintigraphy). At M3, only patients that underwent scintigraphy at the same hospital were accessed ($n = 17$). All patients were instructed to follow a free iodine diet prior to I^{131} therapy and received instructions for oral hygiene, mouthwash with lemon juice and intake of 3 l of water daily during hospitalization and post-therapy for 15–30 days.

Saliva collection and analysis

Whole saliva were collected into a sterile plastic container at 07:00–09:00 a.m. in a quiet and isolated room according to Koseki et al. [15] and Navazesh [16] protocols. All subjects refrained from eating, drinking and oral hygiene for at least 1 h prior to saliva collection. Stimulated salivary samples were obtained during chewing movements using a 1.5 cm standard-size silicone piece for 5 min. All samples were stored at −20 °C until analysis.

The flow rate was measured using a 0.1 mL accuracy syringe and samples were centrifuged for 5 min at 282*g* and 25 °C. After centrifuging, the saliva supernatant was separated and immediately submitted to total calcium and phosphorus determination by a Cintra 6 UV-Visible spectrophotometer (GBC, Australia) using commercial kits (catalogue number 42 and 95; Labtest, Brazil). Calcium concentration was measured by Arsenazo III reaction at 600 nm and phosphate by an acid-molybdate method at 650 nm, according to the manufacturer's instructions, always in triplicate. In every analysis, one standard sample (Wiener Lab, Santa Fe, Argentina) was used to ensure method accuracy. All readings were taken once by a single technician. Method precision was demonstrated by relative standard deviation values obtained within 10% and 20% for phosphate and calcium determinations, respectively (data not shown).

Statistical analysis

The SPSS™ program version 17 (SPSS Inc., Headquarters, Chicago, IL, USA) was used for the statistical analysis. The Wilcoxon signed-rank test was used for analysing the salivary flow rate and calcium and phosphate concentrations. The Fischer's Exact Test was used to analyse the xerostomia and hyposalivation questions. The significance $p < 0.05$ was considered.

Table 1. Characteristics of study subjects.

Sex	
Male	6 (16.2%)
Female	31 (83.8%)
Age (years)	
Mean ± SD	43.37 ± 13.55
Range	14–68
Comorbidities	
Hypertension	3 (8.1%)
Diabetes	4 (10.8%)
Depressive disorders	3 (8.1%)
No systemic diseases	27 (73%)
Medication	
Antidepressant	3 (8.1%)
Antihypertensive	2 (5.4%)
No medication	32 (86.5%)
Habits	
Smoking	2 (5.4%)
Alcoholism	0 (0.0%)
No habits	35 (94.6%)
Total	37 (100%)

SD: Standard deviation.

Results

All 37 patients were diagnosed with well-differentiated thyroid carcinomas and submitted to 100–250 mCi I^{131} doses with a mean age of 43.37 ± 13.55 (mean ± standard deviation). Clinical characteristics are shown in Table 1.

There was no statistically significant difference between the mean values of flow rate of any moment analysed during the study, although when analysing individual data, we could detect hyposalivation (salivary flow rate under 0.7 mL/min) [17,18]) in 13 (35%) patients at M1, 15 (40%) at M2, and 10 (27%) at M3. Examining each patient separately and considering an alteration of at least 10% in individual flow rate, 22 patients had salivary flow reduction between M1 and M2. In those patients analysed at M3, 7 returned to the previous rate found at M1 (Table 2). There was a significant salivary calcium and phosphate reduction between M1 and M2 ($p = 0.023$ and $p = 0.018$, respectively) with an elevation through M3. Salivary flow rate and calcium and phosphate data are shown in Table 3 and Figures 1–3.

Regarding questions related to xerostomia/hyposalivation complications, there were significant differences only between M1 and M2, with a greater number of patients reporting dry mouth and difficulty swallowing food at M2 and less patients with dysphagia and trouble chewing food at M2 (Table 4).

Discussion

Head and neck radiotherapy has been proven to lead to hyposalivation and xerostomia as major side effects when salivary glands are irradiated [9,11]. Similarly, radioactive I^{131} treatments may cause salivary gland impairment with 42.9% of patients suffering from reduced salivary gland function after 1 year of treatment [10]. According to Almeida et al. [19], the ability of salivary glands to eliminate Technetium-99m pertechnetate (in scintigraphy) after iodine treatment diminishes significantly, although salivary flow rate had no association with the same treatment. Otherwise, both studies did not assess the same patients before and after radioactive

I^{131} treatment with the evaluation period varying from 2 months to 10 years post-treatment. Thus, in the present study, saliva samples were collected before, immediately after and about one week post-treatment in order to analyse salivary gland impairment in each patient analysed. It is important to highlight that we had some lost in collecting M3 samples and questions data since some patients did not came back to proceed scintigraphy in the same Nuclear Medicine Service, leading to a limitation of this study.

Eighty-three percent of patients were female since thyroid carcinomas affect more women in a 3:1 (female/male)

Table 2. Individual salivary flow rate.

Patient	M1	M2	M3
1	0.76	0.60[a]↓	0.48[a]
2	0.68[a]	0.48[a] ↓	0.28[a]
3	2.48	2.16↓	2.40↑
4	1.52	0.44[a]↓	
5	1.48	0.76↓	0.92
6	0.60[a]	0.44[a]↓	0.60[a]↑
7	0.76	1.60	
8	3.12	2.60↓	3.48↑
9	1.48	1.28↓	
10	0.88	0.36[a]↓	1.36↑
11	1.20	1.96	
12	1.68	2.40	
13	1.56	1.34↓	
14	1.20	0.80↓	
15	0.84	0.96	
16	3.88	2.75↓	
17	2.24	1.84↓	
18	0.68[a]	0.76↓	
19	0.48[a]	0.72	
20	0.40[a]	1.04	
21	0.78	0.86	0.60[a]
22	1.72	1.20↓	
23	1.00	0.80↓	
24	0.80	1.32	
25	0.64[a]	0.55[a]↓	
26	0.76	1.84	
27	0.60[a]	0.55[a]	
28	0.24[a]	0.64[a]	0.48[a]
29	0.76	0.60[a]↓	0.88↑
30	0.80	0.74	0.76
31	0.64[a]	0.60[a]	
32	0.72	0.55[a]↓	0.45[a]
33	0.48[a]	0.40[a]↓	0.32[a]
34	0.96	0.85↓	1.20↑
35	0.24[a]	0.26[a]	0.30[a]
36	0.36[a]	0.32[a]↓	0.40[a]↑
37	0.48[a]	0.65[a]	0.58[a]

[a]Hyposalivation (salivary flow rate under 0.7 mL/min) [17,18]).
↓≥10% salivary flow reduction ($n=22$ patients).
↑Flow rate returned to previous rate found at M1 or higher ($n=7$ patients).

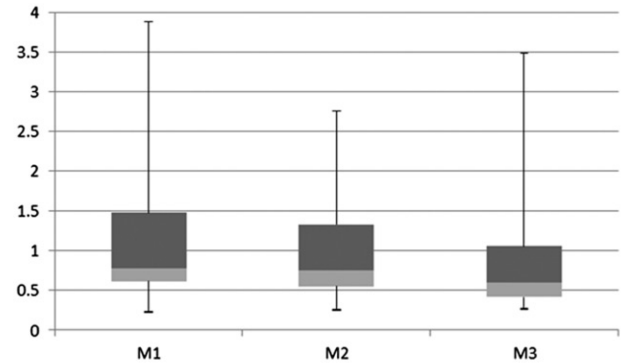

Figure 1. Salivary flow (ml/min).

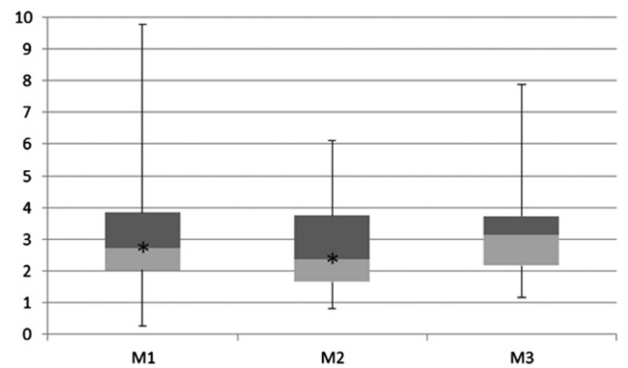

Figure 2. Salivary calcium concentration (mg/dL).

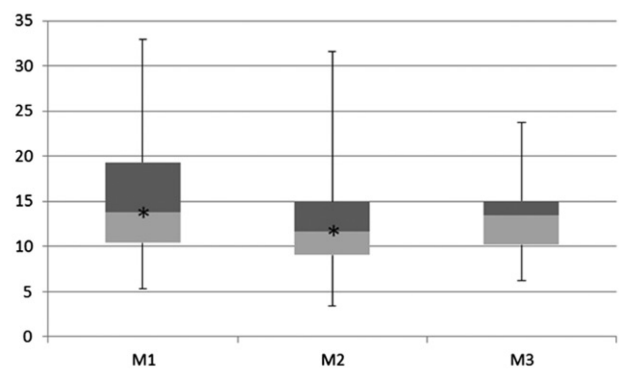

Figure 3. Salivary phosphate concentration (mg/dL).

Table 3. Salivary flow rate and calcium/phosphate concentrations.

				p Value* for		
Salivary	M1 ($n=37$)	M2 ($n=37$)	M3 ($n=17$)	M1 × M2	M1 × M3	M2 × M3
Flow (mL/min)						
Mean ± SD	1.07 ± 0.78	1.02 ± 0.67	0.91 ± 0.84	0.267	0.776	0.276
Range	0.24–3.88	0.26–2.75	0.28–3.48			
Calcium (mg/dL)						
Mean ± SD	3.08 ± 1.83	2.17 ± 1.42	3.14 ± 1.55	0.023	0.868	0.554
Range	0.26–9.78	0.81–6.12	1.16–7.86			
Phosphate (mg/dL)						
Mean ± SD	15.21 ± 6.23	12.27 ± 5.5	13.37 ± 4.87	0.018	0.309	0.193
Range	5.34–32.93	3.38–31.62	6.23–23.78			

SD: Standard Deviation; *Wilcoxon signed-rank test; M1: 30–45 days before I^{131} therapy; M2: 1–2 day(s) after I^{131} therapy, when patients left hospital; M3: 7–10 days after I^{131} therapy.

Table 4. Percentage of positive answers for xerostomia/hyposalivation's questions in each moment.

Questions	M1	M2	M3	p Value* for M1 × M2	p Value* for M1 × M3
The amount of saliva in your mouth seems reduced?	28.6% ($n = 35$)	58.6% ($n = 28$)	54.5% ($n = 11$)	0.236 ($n = 27$)	0.444 ($n = 9$)
Do you fell your mouth dry?	41.7% ($n = 36$)	67.9% ($n = 28$)	73.3% ($n = 15$)	*0.013* ($n = 27$)	0.251 ($n = 14$)
Do you have trouble to:					
• Chew your food?	21.6% ($n = 37$)	17.9% ($n = 28$)	18.2% ($n = 11$)	*0.015* ($n = 28$)	0.055 ($n = 11$)
• Swallow the food?	11.1% ($n = 36$)	20.7% ($n = 29$)	9.1% ($n = 11$)	*0.011* ($n = 28$)	§
• Talk?	8.3% ($n = 36$)	3.6% ($n = 28$)	20% ($n = 10$)	0.074 ($n = 27$)	1.000 ($n = 9$)
• Taste food?	11.1% ($n = 36$)	13.3% ($n = 30$)	10% ($n = 10$)	0.080 ($n = 29$)	0.111 ($n = 9$)
Does your dental status changed after radioiodine therapy?	NA	63.3% ($n = 30$)	92.3% ($n = 13$)	NA	NA

Numbers in parentheses represent the amount of responses analysed; Note that not all patients answered all questions since the questionnaire was self-applicable. NA: not applicable; *Fischer's Exact Test; M1: 30–45 days before I^{131} therapy; M2: 1–2 day(s) after I^{131} therapy, when patients left hospital; M3: 7–10 days after I^{131} therapy.

ratio [20]. Although there was no salivary flow rate difference between any moment examined, when considering each patient individually, we cannot discard that 22 patients had a flow reduction at M2, with only seven patients showing salivary flow normalization at M3, when compared to M1 (flow rate near or above value found at M1). In such analysis, other salivary flow influencing factors were rejected, such as medication use or previous hyposalivation status of patients, and strictly considering the I^{131} treatment effect. To explain these results, it can be hypothesized that some patients may eliminate I^{131} more slowly, submitting the salivary glands cells to extended radiation exposure, which can be responsible for long lasting hyposalivation. The use of lemon stimulation can improve this elimination through the saliva, but since this is a standard protocol followed by all patients, in the present study, it was not possible to assess its effect on salivary flow and the exact amount of lemon used by each patient could not be controlled. All these results may reflect salivary gland radiosensitivity, with potential hypofunction and oral complications. Although there are no studies showing I^{131} effects on salivary gland cells, it is known that it can be responsible for thyroid cells necrosis and oedema [21], and so the same effects over salivary gland cells may be expected. In patients analysed in the present study, none showed any clinical disturbance related to hyposalivation such as candidiasis or mucosal dryness.

Although water is the major salivary component, compounding up to 99% of its total volume, inorganic and organic components such as sodium, potassium, calcium, magnesium, bicarbonate, phosphates, immunoglobulins, proteins, enzymes, and mucins play an important role in salivary function [22]. This fluid consists of a reserve for calcium and phosphate, which are essential for the enamel remineralization of initial carious lesions [23]. Since both ions were found to be reduced in the saliva of patients with active caries [22–25], the present study evaluated their concentrations before and after I^{131} therapy in order to estimate caries susceptibility related to thyroid cancer treatment. Average concentrations significantly decreased after treatment, with an increase at M3 (3.08 → 2.17 → 3.14 mg/dL for calcium and 15.21 → 12.27 → 13.37 mg/dL for phosphate). While there was no statistical difference between M2 and M3, the results showed a clear increase in both ions about one week after treatment, suggesting that a transient period of lower calcium and phosphate concentrations exists with a tendency for normalization in almost one week after therapy. It is important to note that other involved factors such as pH and buffer capacity were not measured in the present study, but can influence the dental demineralization/remineralization processes. In addition, since dental caries injuries require a longer time to develop and be detected, it was not possible to identify any new cavity or white spot lesion at M3, and a long term evaluation was not possible since almost all patients did not return to the same service where the radioiodine therapy was performed and we were unable to access them. However, this early calcium/phosphate reduction may contribute to dental erosion initiation and/or progression of preinstalled lesions, which can be unleashed by the lemon used to stimulate salivary I^{131} elimination. Although no patients related dental sensibility that could be related to dental erosion in the study, it is important that the dental assistant be aware and take precautions for its prevention or treatment during and immediately after iodine treatment.

Although several papers showed a higher xerostomia report in these patients [8,10,26], a significant difference was not observed between any analysed moment when the patients were asked if the amount of saliva in their mouth seemed reduced. But when asked specifically about feeling dry mouth (xerostomia) it was possible to determine a higher number of patients with positive answers at M2, indicating that this symptom can be considered an early radioiodine therapy side effect. Similarly, a higher swallowing difficulty right after iodine application was observed, an effect that can be a result of both hyposalivation and/or local effect of I^{131} over thyroid gland remnants such as inflammatory oedema. Other question showed significant difference between M1 and M2 such as chewing food (lower complaint at M2), but this result needs to be considered with caution because other unknown factors may play a role.

Likewise, salivary flow rate modification, associated xerostomia and decrease in calcium/phosphate concentration can be associated to the immediate radioiodine side effects, at least in some patients, with a trend to subsequent normalization, which can be explained by a progressive I^{131} elimination and possible cellular damage restoration. Accordingly, it's important to highlight the dentist role during thyroid cancer treatment in order to prescribe artificial saliva, higher water intake, and oral hygiene instructions, as well as the removal of infectious/traumatic foci that associated to hyposalivation can contribute to the deterioration of oral health.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The authors declare that this study has been independently reviewed and approved by an ethical board.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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