Evaluation the early effects of single high dose radioiodine therapy on lacrimal gland function

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► ***Original article***

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Revised: July 2013
Accepted: Dec. 2013

Int. J. Radiat. Res., October 2014; 12(4): 319-324

ABSTRACT

***Background*:** The therapeutic administration of ^{131}I for thyroid remnant ablation and for metastases comes up with some adverse effects. This study was conducted to investigate whether single high dose radioiodine therapy affects lacrimal gland functions or not. ***Materials and Methods*:** Seventy-eight eyes of 39 patients, who were diagnosed as differentiated thyroid carcinoma, were objectively tested with Schiermer's test and tear film break-up time test; before and 1 and 6 months after high dose (≥ 3700 MBq) ^{131}I therapy. ***Results*:** The median values of pre-treatment Schiermer's test were 10.00 mm and 9.60 mm for right and left eyes, respectively. At the post-treatment first and sixth months, no significant change was observed in the median values of Schiermer's test in both eyes (p= 0.189 and p=0.085, respectively, Friedman test). The median values of pre-treatment tear film break-up time test were 9.15 sn and 9.20 sn for right and left eyes, respectively. The median values of post-treatment tear film break-up times reduced at first and sixth months and the difference between the pre-treatment and post-treatment values were significant in both eyes (p=0.020 and p=0.022 for right and left eyes, respectively, Friedman test). ***Conclusion*:** Impairment of goblet cell function occurs early after administration of single high dose ^{131}I application. However, reduction in tear secretion from lacrimal gland is not observed.

Keywords: *^{131}I, lacrimal gland, dysfunction, therapy, thyroid cancer.*

INTRODUCTION

The systemic administration of 131-sodium or potassium iodide (^{131}I) is a mainstay therapy for differentiated thyroid carcinoma. It is used for thyroid remnant ablation, and also for treatment of locoregional recurrences or distant metastases because of its trapping by metastatic foci of thyroid cancer. However, apart from thyroid tissue, ^{131}I is also actively concentrated by the nasal mucosa, salivary glands, lactating breast and stomach because of the presence of similar ^{131}I uptake mechanism in these organs. This nonthyroidal accumulation of ^{131}I is responsible for some of the adverse reactions observed after treatment. The most frequent one is sialoadenitis with symptoms of dry mouth and altered taste and objective salivary gland parenchymal dysfunction has been documented in the literature [(1)].

Secretion of ^{131}I in tears was first shown by Bakheet *et al.* [(2)]. Accumulation of ^{131}I in a patient's disposable contact lenses was reported in a case report after that [(3)]. However, few studies investigating the effect of ^{131}I on lacrimal gland function exists in the literature. In the studies by Zettinig *et al.* [(4)] and by Fard-Esfahani *et al.* [(5)], a group patient who received high dose ^{131}I therapy was compared with a controlled group. Without objective testing the lacrimal gland function before ^{131}I therapy, lacrimal gland

function impairment and reduced tear secretion was reported in both of these studies and lacrimal gland dysfunction was attributed to ^{131}I. By Solans *et al.* [6], lacrimal and salivary gland function was investigated on a 3-year-follow up study by yearly examinations after the therapy, but early effects of high dose ^{131}I therapy was not assessed.

Human tear consists of a mixture, comprising the secreted substances from principal lacrimal gland and various accessory lacrimal glands including goblet cells [7]. Principal lacimal gland produce aqueous layer of tear film and its function is evaluated with Schiermer's test. Goblet cells are responsible from the stability of tear film and their function is assesed by tear-film break up time test.

In this study, we prospectively evaluated the early effects of single high dose (≥ 3700 Megabecquerel) ^{131}I therapy on the function of lacrimal glands. Quantitative assessment of the functions of lacrimal glands were performed by Schiermer's test and tear film break-up time test, before and short term after high dose radioiodine therapy

MATERIALS AND METHODS

From September 2011 to January 2013, patients who were referred to Nuclear Medicine department for high dose ^{131}I therapy were prospectively evaluated in this study. All patients were diagnosed as differentiated thyroid carcinoma. ^{131}I was orally applied to destroy remnants or metastases. Post-therapy whole body scan and spot imaging were performed in all patients with a double headed gamma camera (Siemens, e.cam Signature, Germany) equipped with a high energy collimator.

Objective lacrimal gland function was evaluated before treatment and 1 and 6 months after high dose ^{131}I therapy in every patient. Each patient's pre and post therapy ophthalmological examination was performed by the same ophthalmologist at the same conditions. Pre-treatment examinations were performed before thyroid hormone withdrawal and patients were on thyroid hormone replacement therapy at the time of post-treatment evaluations.

Lacrimal gland function was assesed by Schiermer's test and tear film break-up time test. In order to prevent reflex stimulation, Schiermer's test was performed with local anestehesia and 0.5 % proparacain hydrochloride was used. Schiermer strip (Tear touch, London, UK) was inserted into the temporal side of the lower conjunctival fornix. Five minutes later, the paper strip was removed and wetted length in millimeters was recorded. For the measurement of the tear film stability, tear film break-up time test was used. The lacrimal fluid was stained with fluorescein dye (Fluorescein Sodium, Optitech) and the patient was asked to blink several times. The end point was recorded in seconds at the first appearance of dry spot in the precorneal tear film.

Subjective symptoms were evaluated using a patient questionnaire before and after the therapy. All study participants were asked about the presence of dry eye symptoms including foreign body sensation, burning sensation, itching and red eyes.

All patients with symptoms of dry eye or with factors known to cause eye dryness (contact lense using, autoimmune disorders, head and neck radiotherapy, medical treatment with drugs that can cause dry eye), patients with <5 milimeters (mm) / 5 minutes (min) pre-treatment Schiermer's test values or with <5 seconds (sn) pre-teratment tear film break-up time test values, were excluded from the study. The study was approved by the ethics committe of Selcuk University, Faculty of Medicine (No: 2011-53).

Statistical analysis was performed using SPSS (SPSS for Windows, version 16.0). The results are given as mean ± standard deviation and median (range). The comparison of pre-treatment and post-treatment values of left and right eyes were assessed by Friedman test. Wilcoxon signed test was used for subgroup analysis. A P value <0.05 was considered significant.

RESULTS

Pre-treatment lacrimal gland evaluation was performed in 42 patients who were referred to

nuclear medicine department for ^{131}I therapy. Objective pre-treatment ophthalmological examination revealed abnormal Schiermer's test values for both eyes (<5 mm/5 min) in 3 of them, so the study was conducted over 78 eyes of 39 patients (7 men, 32 women; age range 20-79 years; mean age, 43±13).

One patient was diagnosed as follicular carcinoma, 6 as papillary carcinoma folliculary variant and remaining 32 patients had classical papillary carcinoma. In 2 patients with papillary carcinoma, lymph node metastases were present so they received 5550 Megabecquerel (MBq) ^{131}I. In the remaining 37 patients, 3700 Megabecquerel (MBq) ^{131}I was applied to destroy remnants. None of the post therapy scans revealed ^{131}I uptake outside the thyroid bed (figure 1).

The median values of pretreatment Schiermer's test were 10.00 mm (5-15) and 9.60 mm (5-18) for right and left eyes, respectively. At the post-treatment time, the median value of Schiermer's test was 9.33 mm (2-20) at the first month and 11.00 mm (3-25) at the sixth month for right eyes (p=0.189, Friedman test). For left eyes, the median values of post-treatment Schiermer's test were 9.25 mm (2-20) and 11.33 mm (3-20) at the first and sixth months, respectively (p=0.085, Friedman test). The difference between the pre-treatment and post-treatment first and sixth months Schiermer's test values was not significant for right and left eyes.

The median values of the pre-treatment tear film break-up times were 9.15 sn and 9.20 sn in right and left eyes, respectively. At the post-treatment first and sixth months, median values of tear film break-up times were 8.09 sn and 8.11 sn respectively for right eyes (p=0.020, Friedman test) and 8.90 sn and 7.93 sn for left eyes (p=0.022, Friedman test). In right eyes, the difference between the median break-up time values of pre-treatment and post-treatment first and sixth months were calculated as significant (Wilcoxon signed test, p=0.042 and p=0.023, respectively). Whereas difference between the median values of post-treatment first and sixth month break-up times was not significant

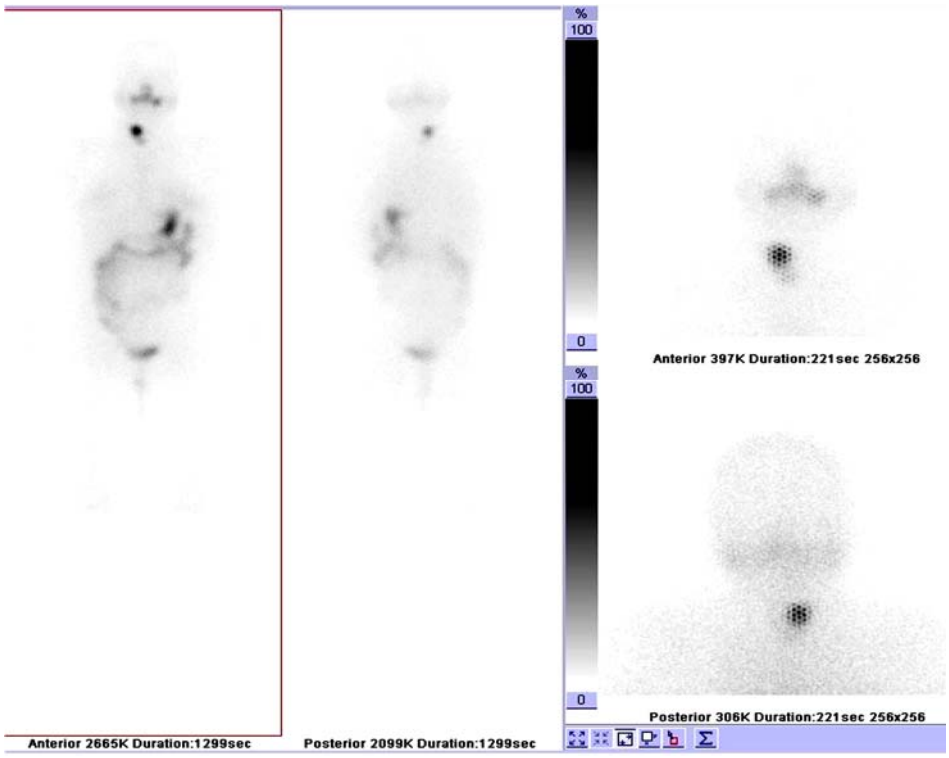

Figure 1. A forty-year-old female patient with papillary carcinoma**.** After receiving 3700 MBq ^{131}I for remnant ablation, physiological radiotracer distribution outside thyroid bed was observed on post therapy scan.

(Wilcoxon signed test, p=0.492). For left eyes, the difference between median values of pre-treatment and post-treatment sixth month break-up times was significant (Wilcoxon signed test, p=0.005). However, the difference between the median values of pre-treatment and post-treatment first month and the difference between the median values of post-treatment first and sixth month was not significant (Wilcoxon signed test, p= 0.08 and p=0.116, respectively). The results of pre-treatment and post-treatment lacrimal gland functions of right and left eyes are shown in table 1 and table 2.

Five patients suffered from subjective symptoms and in the remaining 34 patients, no symptoms were recorded. In 3 patients only redness was noted, in 1, both itching and burning sensation was present and in the other one; all of the dryness symptoms including redness, burning and foreign body sensation were present. Because of the low number of patients with symptoms of dryness, statistical significance of difference of lacrimal gland functions between symptomatic and asymptomatic patients was not evaluated.

DISCUSSION

^{131}I therapy is generally well tolerated but the procedure has a number of potential early and late sequelaes. While gastritis, radiation thyroiditis, tumour swelling and sialoadenitis are known as early side effects of radioiodine; pulmonary fibrosis and bone marrow depression are reported as late sequelaes of this therapy [8]. Among these, involvement of salivary glands after ^{131}I is the mostly investigated one and parotid and submandibular gland dysfunction has been demonstrated before [9]. The impairment of parotid gland has been reported as worse than submandibular gland which was attributed to high concentration of serous acinar cells in parotid glands [9].

Like salivary glands, lacrimal glands also contain serous acini, a grouping of serous cells. This serous cells produce a watery serous secretion which can be measured by Schiermer's test. There are also goblet cells in conjunctiva which are responsible from the mucoid fraction of human tear and their function also be quantified by tear film break-up time test. Although normal values for Schiermer's test and tear film break-up time test had been reported, the rate of tear secretion is affected by age and hormonal status [7,10]. So individual factors must be taken into consideration and pre-treatment test must be performed while evaluating the effects of madications on lacrimal gland functions.

In our study, tear secretion rate was not reduced early after high dose radiodine and the difference between the pre-treatment and post-treatment results of Schiermer's test values was not significant. Our results are discordant with the results of other studies reported before. In the study by Solans *et al.* [6], administered

Table 1. The results of pre-treatment and post-treatment values of ophthalmological examination for right eyes.

	Pre-treatment		1st month		6th month	
	Mean	*Median*	*Mean*	*Median*	*Mean*	*Median*
Schiermer's test (mm)	9.87 ± 3.65	10.00	9.92 ± 5.20	9.33	11.53 ± 5.32	11.00
Break-up time (sn)	9.53 ±3.56	9.15	8.43 ±3.05	8.09	8.07 ± 2.64	8.11

Table 2. The pre-treatment and post-treatment results of Schiermer's test and tear film break-up test for left eyes.

	Pre-treatment		1st month		6th month	
	Mean	*Median*	*Mean*	*Median*	*Mean*	*Median*
Schiermer's test (mm)	9.94 ± 3.76	9.60	10.30 ±5.05	9.25	11.74 ± 4.54	11.33
Break-up time (sn)	9.71 ± 3.10	9.20	9.10 ± 3.58	8.90	8.02 ± 3.04	7.93

activities ranged between 925 MBq and 18.5 GBq, yearly examinations were performed and early effects of ^{131}I was not evaluated. Higher administered cumulative activities and longer interval between ^{131}I therapy and ophtalmological examination may be the most likely explanations for the different results of the two studies. Koca *et al.* [11], performed a pre-treatment evaluation of lacrimal gland function before treatment and reported a decrease in the value of Schiermer's test even after low-dose ^{131}I therapy in a study which, ^{131}I was applied for hyperthyroidism. Although absence of thyroid opthtalmopathy before and after the therapy had been noted, post-treatment levels of thyroid hormones, which are well known to be associated with dry eye syndrome has not mentioned. Lacrimal gland has specific thyroid hormone receptor and hypothyroidism impairs lacrimal gland function [12]. So the change in the values of Schiermer's test after ^{131}I may be associated with hormonal dearengements rather than direct effect of iodine on the glands. This was suggested before by Markitziu *et al.* [13] and may also explain the difference between our results and the results of that study. Decreased tear production was reported after high dose ^{131}I also by Zettinig *et al.* [4] and by Fard-Esfahani *et al.* [5] but in these two studies, patients with history of ^{131}I therapy was compared with control individuals and pre-treatment objective testing was not performed. In our study, all of the patients were asymptomatic before therapy and moreover, 9 patients' Schiermer's test values were lower than 10 mm/5 min, already before ^{131}I administration. This cut-off value was determined as abnormal in that studies. Without examing the pre-treatment value, the result of post-treatment evaluation can not be attributed to ^{131}I.

However, tear-break-up time was reduced and the change between pre-treatment and post -treatment values was significant. Reduction of goblet cell function was observed shortly after ^{131}I administration and persisted 6 months after the therapy. Decreasement in post-treatment values of tear film break-up time test was also reported by Koca *et al.* even after low doses of ^{131}I [11]. Lacrimal gland is localized only in the supraorbital part of the orbita but goblet cells are found widespread in conjunctive. Because of this localization difference, goblet cells may be affected diffusely with radioactive tear and they may be more radiosensitive than lacrimal gland. In the study by Solans *et al.* [6] decrease in tear break up-time test was reported in yearly evaluations after high dose ^{131}I but we showed that goblet cells are affected early after single high dose ^{131}I. However, we could not evaluate the lacrimal gland function far beyond 6 months after the therapy. So whether tear rate reduction appears on late term or goblet cell dysfunction is transient or not, could not be assessed. This can be considered as a weakness of our study. Since decreasement in Schiermer's test values was not observed after therapy, there were only few patients with dryness symptoms in our study. We think that, abnormality noted in tear film break-up time test is not solely enough for the diagnosis of dry eye.

In conclusion, reduction in tear secretion rate is not an early side effect of single high dose ^{131}I therapy. Goblet cell dysfunction may be observed however. Further studies with longer post-treatment follow-up periods are need to evaluate whether impairment of goblet cell function persists or it is a transient side effect.

Conflict of interest: *Declared none.*

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