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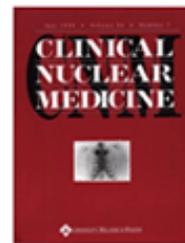
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The Effect of High-Dose Radioiodine Treatment on Lacrimal Gland Function in Patients With Differentiated Thyroid Carcinoma

Armaghan Fard-Esfahani, MD, Hossein Mirshekarpour, MD, Babak Fallahi, MD, Mohammad Eftekhari, MD, Mohsen Saghari, MD, Davood Beiki, PhD, Kianoush Ansari-Gilani, MD, and Abbas Takavar, PhD

Purpose: There are a limited number of case reports confirming the radioiodine (I-131) presence in tears and only a few case reports of lacrimal gland dysfunction after I-131 therapy. This study was designed to clarify whether lacrimal gland function can be affected by I-131 therapy.

Materials and Methods: We studied 100 eyes of 50 patients who had received high doses of I-131 for treatment of differentiated thyroid carcinoma and 100 eyes of 50 age- and sex-matched control individuals without a history of interfering conditions. The exposed group was studied at least 3 months after their last I-131 therapy. Dry eye symptoms and Schirmer test values (wetting level in millimeters per 5 minutes) of an exposed group were compared with those of an unexposed group.

Results: Fifty-one percent of the exposed eyes and 50% of the unexposed ones revealed at least 1 of the dry eye symptoms. There was no significant difference in symptoms between 2 groups, except for burning sensation and eye redness, which were significantly higher in the exposed eyes. A lower Schirmer test value was noted in the exposed group, 14.5 ± 10.8 mm, when compared with that in controls, 18.2 ± 11.0 mm ($P = 0.016$), and the relative risk of an abnormal Schirmer test in exposed cases to control group was 1.78 ± 0.62 . Correlation coefficient analysis showed no significant relationship between Schirmer test values and cumulative doses of administered I-131.

Conclusions: Reduction in the tear secretion from lacrimal glands is seen after high-dose I-131 therapy; however, their symptoms are no greater than an unexposed population.

Key Words: complication, iodine-131, lacrimal glands, radioiodine therapy, thyroid cancer, I-131

(*Clin Nucl Med* 2007;32: 696–699)

Received for publication March 3, 2007; revision accepted May 23, 2007. From the Research Institute for Nuclear Medicine, Medical Sciences/University of Tehran, Shariati Hospital, Tehran, Iran. Supported by the Medical Sciences/University of Tehran (grant no. 2021). Reprints: Babak Fallahi, MD, Research Institute for Nuclear Medicine, Shariati Hospital, Kargar Shomali Ave., PC 14114, Tehran, Iran. E-mail: bfallahi@sina.tums.ac.ir.

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ISSN: 0363-9762/07/3209-0696

It is more than 50 years since I-131 has been used as a valuable treatment in thyroid diseases including hyperthyroidism and differentiated thyroid carcinomas (DTC).¹ Salivary glands are among the organs that show physiologic uptake and excretion of I-131.¹ Radiation damage to salivary glands is suggested and supported by several studies.^{2–4} Although the secretion of radioiodine (I-131) in tears is not unexpected, there are only a few investigations in this field. Bakheet et al semiquantitated I-131 secretion in the tears of a thyroid-ablated patient with an artificial eye and showed that appreciable amount of ingested I-131 could be secreted in tears.⁵ A case of I-131 accumulation in a patient's disposable contact lenses after receiving radioactive iodine was also reported.⁶ Only a few studies have been performed to assess the I-131 effect on lacrimal gland function. Schirmer test, first described in 1903, is a simple and practical clinical way of measuring tear secretion.⁷ Using the Schirmer test, this study was planned for quantitative evaluation of lacrimal gland function in patients with a history of I-131 therapy for DTC.

PATIENTS AND METHODS

This is a historical cohort study comparing I-131-treated (exposed) group consisting of 100 eyes from 50 patients (14–72 years, mean: 44.0 ± 14.0), including 10 men (20%) and 40 women (80%), and the untreated control group (unexposed) consisting of 100 eyes of 50 patients [9 men (18%) and 41 women (82%), 13 to 72 years, mean: 44.3 ± 13.2]. This prospective study was approved by the ethics committee of Tehran University of Medical Sciences, and consent forms were obtained from all patients. The exposed group was selected from patients with thyroid cancer who received therapeutic doses of I-131 (100–450 mCi once or more) to destroy remnants or metastases after thyroidectomy. For all patients, the study was performed after at least 3 months of the last I-131 therapy when they were in a euthyroid state. The unexposed group (control) consisted of 100 eyes of age- and sex- matched euthyroid cases, without a history of I-131 therapy. All patients with a history of any other potential causes of eye dryness including autoimmune disease (with possible effect on lacrimal glands), using contact lenses, taking drugs inter-

fering with lacrimal gland function, such as antihistamine and psychotropic drugs, lacrimal gland injuries and eye trauma of any type (physical, chemical, thermal, or iatrogenic), radioactive therapy for diseases other than thyroid cancer, head and neck radiotherapy, diseases involving the nervous system of lacrimal glands, diabetes mellitus, androgen or other hormonal therapies, pterygium, Graves' disease with or without ophthalmopathy, blepharitis, and any other conditions, which may reduce tear production or result in rapid evaporation (air conditioners, low humidity, excesses tears, lipids), were excluded from each of these 2 groups.

In this study, the subjective symptoms of dry eye including a foreign body or sand sensation, burning sensation, photophobia, itching, artificial tear consumption, sticky eyelids at morning, red eyes (without a known cause like weather conditions), and eye irritation along with the objective finding obtained by Schirmer test, in the exposed group, were compared with those in the unexposed group.

Objective assessment for lacrimal gland function was performed by Schirmer test defined as wetting of a special strip of Whatman filter paper in terms of millimeter per 5 minutes.

Statistical analysis was done using the Student *t*-test for comparing quantitative variables with normal distribution, such as mean age and Schirmer test values, between groups. χ^2 and Fisher exact test were used for comparing distribution of qualitative variables such as dry eye symptoms between groups. Also a qualitative analysis with Kruskal–Wallis *H*-test was used by subgrouping the eyes concerning the ordinal levels of wetting as 0 to 4, 5 to 9, ≥ 10 mm/5 min to define whether the levels of wetting in exposed eyes are different from the control group. Pearson's correlation coefficient test was applied for analyzing the relationship between the cumulative dose of I-131 and Schirmer test values. A *P* value < 0.05 was considered significant for each statistical analysis. In addition, relative risk was calculated in a confidence interval of 95%.

RESULTS

No significant difference was noted between the mean age of the exposed group (44.0 ± 14.0) and the unexposed group (44.3 ± 13.2) ($P = 0.868$).

The data for subjective symptoms of dry eye in the exposed and unexposed groups are shown in Table 1 and reveal that only 2 symptoms (eye redness and burning sensation unrelated to light) were significantly higher in the exposed eyes. From 9 exposed eyes complaining of eye redness, Schirmer test result was abnormal in only 2 (1 patient). Also among the 10 eyes with burning symptoms, only 1 patient (2 eyes) revealed an abnormal Schirmer test. There was more than 1 symptom in 51% of cases of the exposed group, which was almost the same as the unexposed group 50% ($P = 0.888$). Totally, the commonest symptom for both groups was eye itching (27% in the exposed and 33% in the control group) followed by a burning sensation (18% in the exposed group and 22% in the control group). Our objective data obtained by Schirmer test (defined as wetting of a special strip in terms of millimeter per 5 minutes) were analyzed by 3 methods.

The mean value of Schirmer test in the exposed group was 14.5 ± 10.8 mm, whereas in the unexposed group was 18.2 ± 11.0 mm ($P = 0.016$).

Considering strip wetting ≥ 10 mm as normal and less than that as abnormal, 41% of the exposed eyes versus 23% of the unexposed eyes had an abnormal test ($P = 0.006$), and the relative risk of abnormal Schirmer test in the exposed group proportionate to the control group was 1.78 ± 0.62 ; confidence interval = 95%. Qualitative analysis of Schirmer test values revealed a significant difference between 2 groups of exposed and unexposed eyes, $P = 0.004$ (Table 2). Although the Schirmer test values were significantly lower in eyes exposed to any high doses of I-131, Pearson's correlation coefficient analysis showed no significant relationship between Schirmer test values (millimeter per 5 minutes) and cumulative doses of administered I-131 (mCi) ($r = -0.23$, $P = 0.12$).

TABLE 1. Comparison Between Exposed (Received I-131) and Unexposed (Not Received I-131) Groups Concerning Dry Eye Symptoms

Eye Symptoms	Exposed Group n = 100		Unexposed Group n = 100		Total n = 200		Statistical Significance of Difference <i>P</i>
	N	%	N	%	N	%	
Foreign body sensation	6	6.0	2	2.0	8	4.0	0.279 NS
Burning sensation (related to light)	18	18.0	22	22.0	40	20.0	0.480 NS
Eye itching	27	27.0	33	33.0	60	30.0	0.355 NS
Using artificial tear	4	4.0	6	6.0	10	5.0	0.516 NS
Eyelids stickiness in the morning	5	5.0	0	0.0	5	2.5	0.059 NS
Eye redness (repetitive)	9	9.0	0	0.0	9	4.5	0.003
Burning sensation (unrelated to light)	10	10.0	0	0.0	10	5.0	0.001
Eye stimulation with smoking	12	12	6	6.0	18	9.0	0.138 NS
Epiphora without stimulation	2	2.0	0	0.0	2	1.0	0.497 NS

N indicates number of eyes; NS, nonsignificant.

TABLE 2. Qualitative Analysis of Schirmer Test in Exposed and Unexposed Groups

Schirmer Test Values	Exposed		Unexposed		Total	
	N	%	N	%	N	%
0–4 mm	21	21	6	6	27	13.5
5–9 mm	20	20	17	17	37	18.5
≥10 mm	59	59	77	77	136	68
Total	100	100	100	100	200	100

N indicates number of eyes.

DISCUSSION

The 2 studied groups (exposed and unexposed) were age- and sex-matched without any confounding effect on the results. There was no significant difference between the 2 groups in subjective dry eye symptoms ($P = 0.407$) totally; however, comparing each symptom in 2 groups, 2 symptoms including redness and a burning sensation had a significantly higher frequency in the exposed group, $P = 0.003$ and 0.001 , respectively.

The commonest symptom in the dry eye syndrome is a foreign body sensation.⁷ Although this finding was 6% in our exposed group versus 2% in the unexposed group, the difference was not statistically significant ($P = 0.279$).

In a study by Hay et al, too, only weak associations were found between self-reported symptoms of dry eyes and dry mouth and objective measures.⁸ In the present study, the objective assessment was performed by the Schirmer test, which evaluates total lacrimal gland function (major and minor lacrimal glands).

Schirmer test results were analyzed in 3 ways. In all 3 ways including (a) quantitative analysis by quantitation of the mean value of Schirmer test in the exposed and unexposed group, (b) qualitative analysis considering the strip wetting more than 10 mm as normal and less than that as abnormal, and (c) qualitative analysis by subgrouping the patients concerning the degree of wetting, the final results established that the function of lacrimal glands in exposed eyes (patients who had received I-131) was significantly lower than that of the control group. In the last mentioned method of analysis, the greatest difference between 2 groups was observed in the subgroup of 0 to 4 mm/5 min wetting (21% in the exposed group vs. 6% in the unexposed group), which means I-131 therapy not only resulted in lacrimal gland dysfunction, but also this effect was severe.

A few other previous studies and case reports also reported dry eye condition as a complication of I-131 therapy.^{4,9,10} Schirmer test is a precise and reliable method to evaluate tear flow even in severe tear reduction.⁷ The results of Schirmer test in the present study do not reveal whether major, minor, or both groups of lacrimal glands are affected by I-131. However, considering the fact that minor glands are responsible for basal tear secretion (resection of major glands does not induce dry eye),⁷ as there is no significant difference between 2 groups in dry eye symptoms in this study, it is likely that major glands are mainly involved.

Epiphora due to nasolacrimal drainage system obstruction (NDSO) has also been reported by Kloos et al¹¹ with an incidence of 3% among 390 patients after I-131 therapy. The patients with NDSO had received more I-131 therapy for persistent disease than is typically seen with DTC. In this report, all patients with epiphora had evidence of NDSO disease after a median cumulative dose of 433 mCi (16,000 MBq), and symptomatic obstruction was seen in only 4 cases (about 2%) of patients after being treated with less than 433 mCi. Similarly, 2% of the cases in our study who received 100 to 450 mCi showed epiphora without stimulation (Table 1) that may not differ from the incidence of symptomatic obstruction in the general population. To establish a definitive conclusion about the importance of this complaint, a systematic well-designed study with an appropriate control population will be necessary. If a significant association is found between using I-131 and higher incidence of nasolacrimal obstruction, it is still to be ascertained if the obstruction results from local toxicity caused by the passive flow or the active accumulation of I-131 in the lacrimal drainage system.

There was no significant relationship between Schirmer scores (millimeter per 5 minutes) and I-131 cumulative doses from 100 to 450 mCi. As a result, despite the overall effect of high-dose (>100 mCi) I-131 treatment on lacrimal gland function, the degree of loss appears to be unrelated to the dose when it is over 100 mCi (3700 MBq). However, regarding the fact that lacrimal glands may differ in their sensitivity to I-131, more investigations are needed for judgment about the dose threshold of I-131 that may cause reduction in tear secretion and the factors that may be related to lacrimal gland sensitivity.

By further reviewing the results of 21 eyes in the exposed group in whom the Schirmer test results were 0 to 4 mm, we interestingly realized that 4 patients had a history of migraine. On the other hand, in the unexposed group, there was a patient with migraine history whose Schirmer test was totally normal (>10 mm in both eyes). Whether or not migraine has any relations with reduced tear secretion in the exposed group could be a subject for further study.

CONCLUSIONS

Lacrimal gland dysfunction resulting in reduced tear secretion may be seen after high-dose I-131 therapy, but this reduction may not necessarily lead to eye dryness and may not be related to the cumulative administered dose of I-131.

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