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Side-effects of iodized oil administration in patients with simple goiter

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ABSTRACT. The objective of this study was to determine side-effects associated with iodized oil injection in patients with simple goiter. In an iodine-deficient population, 3420 patients with simple goiter, who were not taking supplemental iodine, were chosen for this study. They received a single intramuscular injection of 1 ml iodized oil, containing 480 mg iodide. Clinical and laboratory evaluations were performed every 3 months for one year and every 6 months for the next 4 years. The incidence of hypo- and hyperthyroidism was 0.6% each, with equal prevalence in both sexes. Most cases of hypo- and hyperthyroidism were observed during the first 5 months after the injection. Eight cases of hyperthyroidism were asymptomatic. A further 8 patients had overt thyrotoxicosis and required treatment with methimazole for 18 months. Recurrence of hyperthyroidism was observed in one patient. Five hypothyroid patients were diagnosed only by abnormal thyroid function tests, and 4 cases needed no treatment. Others received T_4 treatment for a mean of 14.5 months. Among 14 T_4-treated patients, recurrence of hypothyroidism occurred in 7 patients after treatment was discontinued. Twenty-nine patients (0.8%) were afflicted with dermatologic complications. The most common dermatologic side-effect was urticarial reaction. In 15 subjects, skin lesions appeared 8 to 14 days after injection. It is concluded that side-effects of iodized oil injection are rare, and in most cases the complications are transient and self-limited. The occurrence of iodine induced hyperthyroidism following iodized oil administration is close to the ratio observed in spontaneous thyrotoxicosis.

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INTRODUCTION

Iodine deficiency is one of the major health problems in the world. It causes a wide range of disorders from simple goiter to overt cretinism with severe psychomotor retardation (1). The main strategy of controlling iodine deficiency disorders (IDD) is universal salt iodization. However, when iodized salt is not available and, in remote areas with severe iodine deficiency, administration of iodized oil has been advised (2).

The most important reported complication of iodized oil injection has been hyperthyroidism, which is prevalent in older patients and in those with multinodular goiter (3-5). Hypothyroidism is seen less frequently than hyperthyroidism and is usually observed as a disturbance in thyroid function tests (4). There have been contradictory reports regarding the appearance of thyroid autoimmunity following iodized oil administration (5, 6). However, no systematic, prospective study has been performed to evaluate side-effects of iodized oil administration.

Goiter is hyperendemic in many parts of Iran (2). In addition to goiter, other IDD, such as impaired physical and intellectual growth, hearing deficit and hypothyroidism, have been reported (7, 8). Since iodized oil injection has been one of the basic strategies of controlling IDD in Iran, this prospective study was conducted to determine the complications of iodized oil injection in patients with simple goiter.

MATERIALS AND METHODS

Patients with simple goiter, entered in this prospective study, had been referred to an endocrinologist, were not taking supplemental iodine and had normal thyroid function test. Only those with clinical and biochemical evidence of hypo- or hyperthyroidism were excluded. Three-thousand six-hundred and fifty-eight patients were recruited into the study during 2 years and 3420 completed the

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study. Patients were residents of Tehran City and suburbs, known to be an iodine deficient region with mean urinary iodine in school-children of 35.8±19.1 µg/l (8). All patients were evaluated before and every 3 months during the first year and every 6 months during the subsequent 4 years after intramuscular injection of 1 ml of iodized oil solution containing 480 mg iodide (Lipiodol, Guerbet, France). In each visit, the patients underwent clinical examination. Symptoms and signs of thyroid dysfunction were sought and approximate thyroid weight was estimated by one of us (F.A.). A 10 ml blood sample was also obtained.

Serum concentrations of T_3, T_4, TSH and T_3 resin uptake were measured by commercial kits from Kodak-Amerlex, England. Antithyroid antibodies including antithyroglobulin and antimicrosomal antibodies were measured by hemoaglutination method by commercial kits from Broughs-Wellcome, England. Reference ranges for serum parameters for euthyroid adult subjects are: T_4: 4.5-12.5 µg/dl, T_3: 80-200 ng/dl and TSH: 0.1-5.0 mU/l.

This study was approved by the appropriate human research review committee and the patients gave informed consent. The difference in quantitative variables before and after injection was evaluated by paired *t* test. *P* value of less than 0.05 was considered significant.

RESULTS

Three-thousand four-hundred and twenty patients with simple goiter including 89.6% femal and 10.4% mal completed the study. Female/male ratio was 9/1. Mean age of patients was 21.5±14.1 years, with a range of 5 to 44 years. During 5 years of follow-up, 3380 patients remained euthyroid. At the onset of the study, they did not differ from the 40 patients who later developed thyroid dysfunction in age, goiter size and nodularity, and serum concentrations of T_4, T_3 and TSH. In patients, who remained euthyroid, mean estimated thyroid weight decreased from 38.5 to 27.1 g in 5 years.

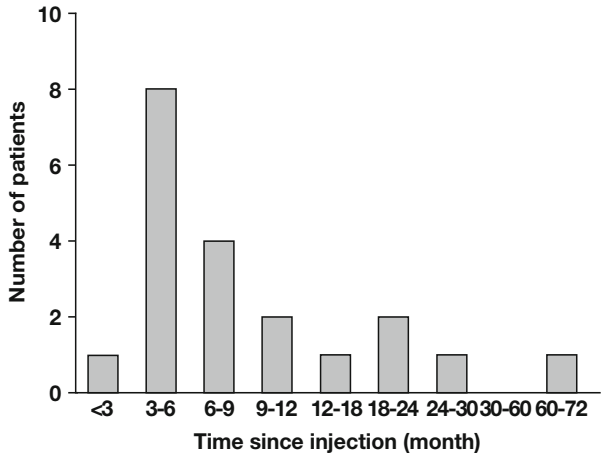

Fig. 1 - *Time of occurrence of hyperthyroidism following iodized oil injection. Twelve out of 20 cases were detected within 3 to 9 months after intervention.*

Hyperthyroidism

Thyrotoxicosis was observed in 20 patients (0.6%) with a male/female ratio of 1/9. Mean age in study population and hyperthyroid patients was not significantly different. Diffuse goiter was observed in 14 cases and nodular goiter in 6 patients. Estimated thyroid weight in 16 hyperthyroid patients did not change significantly after iodized oil injection (36.6±5.1 and 36.1±5.5 g before and after injection, respectively). Most cases occurred during the first 3-6 months after injection (Fig. 1).

The results of serum T_4, T_3 and TSH concentrations in 20 hyperthyroid patients before lipiodol injection and at the time of diagnosis are depicted in Table 1. In 8 patients, hyperthyroidism was detected only by relying on thyroid function tests, whereas the other 12 patients showed some of the following signs and symptoms: palpitation and tachycardia, weight loss, irritability and nervousness, easy fatigability and proximal muscle weakness. Lid lag and stare was observed in thyrotoxic patients, but none had signs of Graves' ophthalmopathy. Prior to iodized oil injection, antithyroid antibodies were

Table 1 - *Serum thyroid hormones and TSH concentrations prior to iodized oil injection and at the time of diagnosis in 20 patients with hyperthyroidism.*

Time	T_4 (µg/dl)	Resin uptake	T_3 (ng/dl)	TSH (mU/l)
Prior to injection	8.7±1.9	29.4±2.4	133±32	1.86±1.4
At the time of diagnosis	17.2±3.9*	34.8±4.7*	339±185*	0.46±0.3*
Normal range	4.5-12.5	25-35	80-200	0.1-5.0

*$p<0.001$, compared to values prior to injection.

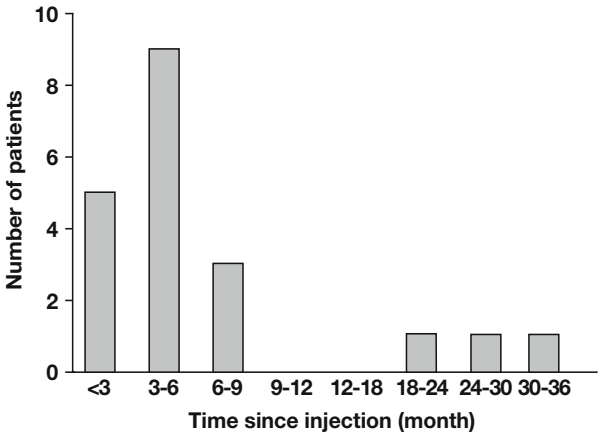

Fig. 2 - *Time of occurrence of hypothyroidism following iodized oil injection. Fourteen out of 20 cases occurred during first 6 months following injection, only 3 cases were detected after 9 months.*

negative in all patients. After injection, only one patient had increased antibodies.
Eight patients did not show any clinical signs of hyperthyroidism and improved without treatment. Palpitation was controlled with propranolol in 4 patients. Eight patients were given methimazole 20 mg per day for 4 weeks and 5-10 mg daily thereafter. The average duration of treatment was 18 months. Recurrence of hyperthyroidism was observed in only one case, that had spontaneous improvement without methimazole therapy.

Hypothyroidism

Hypothyroidism was observed in 20 patients (0.6%) with a female/male ratio 9/1. Diffuse goiter was observed in 14 cases and nodular goiter in 6 patients. Estimated thyroid size was 34.5±5.3 before and 38.4±7.1 g after injection (NS). Most cases of hypothyroidism were observed during the first 6 months after injection (Fig. 2).
The results of thyroid function tests and serum TSH in 20 hypothyroid patients are depicted in Table 2. Fourteen patients had mild symptoms and signs and one patient presented with the typical clinical picture of hypothyroidism. The clinical findings were: mild drowsiness, poly- and hypermenorrhea, decreased appetite, slight weight gain, and mild puffiness. Prior to iodized oil injection antithyroid antibodies were negative in all patients. After injection, in 5 out of 11 patients tested, thyroid antibodies became positive.
Four patients showed improvement of hypothyroidism without receiving any drug therapy. It took 4.0±4.2 months before normalization of thyroid function tests. Pharmacologic therapy with thyroid hormone preparations was necessary in 16 patients. The average duration of treatment was 14.5 months. Recurrence of hypothyroidism was observed in 7 patients necessitating re-administration of thyroid medications.

Dermatologic complications

Skin complications were observed in 29 patients (0.8%) with a mean age of 30.3±9.8 years. The highest incidence rate was observed in age groups of 20-29, 30-39 and 40-49 years with 9, 8 and 7 cases, respectively.
The distribution of the patients concerning the timing of dermatologic complication is illustrated in Figure 3. Most of the complications were observed during the first 8-14 days after injection. Among the 29 patients with dermatologic problems, 4 had diffuse, generalized lesions and 25 only revealed localized lesion at the site of injection.
During the first 24 hours after the injection, there was only one case of dermatologic complication, manifesting as localized swelling, redness, and induration, and being followed by multiple pruritic nodules after a few days. Pathologic examination revealed the lesion to be erythema nodosum. This was successfully treated with topical medications.
During the first 24-48 hours after injection, skin problems were observed in 5 patients, 2 of which had generalized eruptions and 3 had localized lesions. Localized lesions were manifested by swelling, redness, induration, and mild pruritus; whereas generalized eruptions manifested as urticarial lesions and

Table 2 - *Serum thyroid hormones and TSH concentrations prior to iodized oil injection and at the time of diagnosis in 20 patients with hypothyroidism.*

Time	T_4 (µg/dl)	Resin uptake	T_3 (ng/dl)	TSH (mU/l)
Prior to injection	8.5±1.8	28.8±3.1	156±38	1.4±0.7
At the time of diagnosis	2.4±1.9*	26.6±3.0*	84±45*	116±88*
Normal range	4.5-12.5	25-35	80-200	0.1-5.0

*$p<0.001$, compared to values prior to injection.

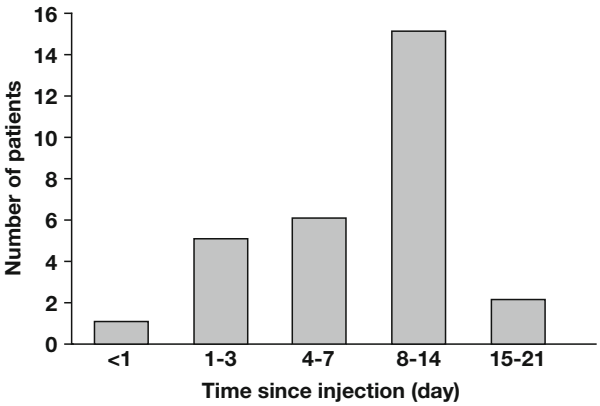

Fig. 3 - *Time of occurrence of dermatologic side-effects following iodized oil injection. More than half of the cases occurred within 8 to 14 days following injection.*

pruritic, edematous and erythematous patches and plaques. Six patients were afflicted with skin problems during days 3-7 after injection. One patient had generalized, erythematous, maculopapular rash and 5 patients had localized lesions.

During 8-14 days after injection, 15 localized skin problems were observed. The lesions manifested as swelling, redness, induration and mild pruritus. The improvement of the lesions took 8.6±4.1 days. Six patients were given corticosteroid treatment and other 9 patients showed improvement of their lesions without any treatment. After 14 days, two cases of localized skin problems were observed. In one of these cases, in addition to the localized lesion, there was a feeling of vaginal pruritus, which was spontaneously resolved.

DISCUSSION

In this study, side-effects of iodized oil injection in euthyroid patients with simple goiter were studied. Two percent of patients developed either hypothyroidism, hyperthyroidism or skin lesions. Thyrotoxicosis and skin complications were self-limited, but hypothyroidism was persistent in a few patients.

The total incidence rate of hyperthyroidism after iodized oil supplementation was 0.6%. This finding is somewhat different from other reports. In a study of 420 Malaysian patients, 8 cases of clinical and 4 cases of biochemical hyperthyroidism (1.7%) were detected (4). Among 960 patients in Ecuador, 3 patients and following 2025 injections in Peru, one case developed hyperthyroidism (9, 10). The present prospective study dealt with a larger population of patients; therefore, the observed difference with other reports can be attributed to the larger population of the study group, differences in patients' selection, or genetic and immunologic backgrounds. In our study, the incidence rate of hyperthyroidism was equal in the two sexes, because the female/male ratios of both study population and hyperthyroids were similar at 9/1. Whereas in a study in Yugoslavia, the male/female ratio of hyperthyroidism increased from 1/10 to 1/6 as a result of iodine supplementation (11). On the other hand, hyperthyroidism did not tend to be more prevalent in higher age groups in our study; in other words, the mean age of the hyperthyroid patients was not greater than that of the study population. Nevertheless, it should be noted that there have been few patients in our study who were older than 40 years.

Present data indicate that it is not possible to predict the occurrence of hypo- or hyperthyroidism on the basis of patients' age, thyroid size, and goiter type. This is in accordance with the study performed in Malaysia (4). Additionally, change in thyroid size following iodized oil injection cannot be used for diagnosis of hyperthyroidism.

The diagnosis of hyperthyroidism has been made in 8 patients only by considering biochemical criteria. In the study conducted in Malaysia, 8 cases with hyperthyroidism had distinct clinical findings (4). The self-limiting nature of complication in asymptomatic patients made no treatment necessary. In other studies, no recurrence of hyperthyroidism has been reported. Observing one such case in our study can be attributed to the long-term follow-up to the patients.

The yearly incidence of hyperthyroidism in women is 0.08% per year (12), and, over 5 years, 0.40% of women may develop hyperthyroidism. Therefore, the 0.6% rate observed in the present study comes very near the spontaneous background level of hyperthyroidism. This is in contrast to the higher incidence of iodide-induced thyrotoxicosis seen in African countries (13).

The presence of antithyroid antibodies following high-dose iodine supplementation has been related to increased prevalence of thyroid autoimmunity by some researchers (14). The incidence rate of such a condition in our study has been low.

The incidence rate of hypothyroidism in our study (0.6%) is greater than that of the previous studies. In a study performed in Sudan, no cases of hypothyroidism were observed following administration of intramuscular iodized oil to 1161 patients and oral iodized oil to 2316 patients (15). In another study performed in Greece, no cases of hypothyroidism were observed in 58 patients with simple goiter who were given iodized oil injection

(14). The increased incidence of hypothyroidism in our study can be attributed to the larger study population, longer follow-up of the patients, or the increased proportion of patients with disturbances in iodine organification (16). It is known that patients with subclinical Hashimoto's thyroiditis will demonstrate irreversible hypothyroidism when exposed to high doses of iodine (17). This possibility cannot be easily ruled out.

The recurrence of hypothyroidism was more prevalent than that of hyperthyroidism; the precise cause of this observation is unknown, but the presence of an underlying thyroid disorder should be considered in these cases. The presence of antithyroid antibodies in some of these cases is a confirmation of underlying thyroid pathology.

The incidence rate of dermatologic complications was 0.8%. The occurrence of dermatologic complications may take days after the injection of the drug. According to the type of allergic reaction, a skin rash is manifested from a few minutes to 24-48 hours after sensitization of the patient (18). The skin problems observed in the patients are: hypersensitivity reaction type I, urticarial lesions, erythema nodosum, and hypersensitivity reaction type III of diffuse maculopapular eruptions.

It is concluded that the incidence rates of thyroidal and extrathyroidal side- effects following injection of iodized oil are low, and it is not possible to predict the occurrence of these complications in different individuals according to the patients' age, thyroid size, and goiter type. The low incidence of these side- effects should encourage the use of iodized oil as a convenient and inexpensive method of iodine supplementation in remote regions and as a therapeutic method in hypothyroid children and adolescents with severe iodine deficiency (19). Follow-up of all patients should be performed in 3- to 6-month intervals for 2 years following injection, and, if symptoms of thyroid derangement occur, biochemical studies should be supplemented.

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