NOTE

Thyroxine Prophylaxis after Bilateral Subtotal Thyroidectomy for Multinodular Goiter

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Abstract. In this study, we investigated the value of thyroxine administration to prevent recurrence after bilateral subtotal thyroidectomy for multinodular goiter. Patients that had benign multinodular goiter were operated on with the same surgical principles: ligation of both superior and inferior thyroid arteries on both sides, bilateral subtotal resection of thyroid gland including all visible nodules. On the 3rd postoperative day, the patients were divided into two groups: with 100 microgram l-thyroxine daily (Thyroxine group) or no therapy (Control group). No recurrences were encountered among 40 patients followed up for 6 months and 20 patients for at least one year. One patient in the control group developed manifest hypothyroidism (5.3%). The mean TSH level of the control group was significantly higher than that of thyroxine group at 1st, 2nd, 3rd, 4th, 5th, 6th, and 12th months. At the end of the first year, the mean TSH level of the control group was four times that of the normal. On the other hand, the mean TSH level of the thyroxine group was within normal limits but not suppressed. In conclusion, we found that the pituitary-thyroid axis did not become normal spontaneously one year after thyroidectomy. Therefore, postoperative thyroxine administration seems to be of value, especially in endemic regions like Turkey.

Key words: Multinodular goiter, Endemic region, Thyroidectomy, Thyroxine, Recurrence

(RECURRENCE of the goiter after surgical treatment in euthyroid patients is still a common problem. Different series revealed high recurrence rates of up to half of the patients in long-term follow-up. Today second surgery accounts for approximately 15% of all thyroidectomies [1]. The complication rate of surgery for recurrence is higher than that of primary operation [2].

Turkey is an endemic goiter country with severe iodine deficiency (total goiter rate >30%) [3]. The recurrence rates of the Turkish series have been quite high. Ibis and coworkers reported a 67.5% overall recurrence rate in a nuclear medicine based study [4].

In a surgical prospective series, Çalık and colleagues found a 17% recurrence rate [5]. Both authors recommended postoperative thyroxine prophylaxis after thyroidectomy for nodular goiter. However, the number of prospective studies that investigate the efficacy of thyroxine administration in our country is very limited. In this paper, we presented the short-term results of a prospective, randomized, non-placebo controlled study on thyroxine prophylaxis after bilateral subtotal thyroidectomy for multinodular euthyroid goiter.

Patients and Methods

The patients who were operated on for multinodular euthyroid goiter in the Fourth Surgical Department of Ankara Numune Teaching and Research Hospital in a two-year period were included in this study. To create a homogenous study popu-
lation a large number of exclusion criteria were used: secondary cases, solitary nodule, hyperthyroidism, thyroiditis, thyroid malignancies, patients younger than 16 years old or older than 70, certain conditions that cause contraindications for exogenous thyroid hormone administration (recent myocardial infarction, serious cardiac disorders, osteoporosis, hypersensitivity to thyroxine, adrenal insufficiency; chronic and mandatory use of some drugs that interact with thyroxine such as anticoagulants, colestramine, sympathomimetics); patients who did not accept to participate in the study, patients who could not return the hospital for periodical control studies due to social-cultural reasons. All the patients had stage II or stage III goiter according to the classification system of the World Health Organization [6]. Indications for operations were compressive symptoms and cosmesis due to large goiters. No patients were suspected to have had thyroid malignancies before the operation. Although all the patients had multinodularity, a low possibility of malignant change was also eliminated by fine needle aspiration biopsy in the preoperative period. Serum levels of FT₃, FT₄, and sTSH were determined in all patients preoperatively (normal levels: FT₃: 1.80–4.60 pg/ml, FT₄: 0.90–1.70 ng/dl, and sTSH: 0.27–4.20 mIU/ml). Every patient was operated by the same surgical principles: superior and inferior thyroid arteries of both lobes were ligated, a bilateral subtotal thyroidectomy including all visible nodules was performed, a remnant of approximately 6–8 gram was left in situ. The removed specimens could not be weighed either in the operating room or in the pathology department because of technical equipment problems in that period.

The patients were divided into two groups before discharge (after doing thyroid function tests for baseline values) on the third postoperative day: 1. Thyroxine group (TG): Patients who were given 100 microgram L-thyroxine sodium daily, and 2. Control group (CG): Patients who were given no medication or placebo. Thyroid function tests were then repeated on the 7th day, and in the 1st, 2nd, 3rd, 4th, 5th, 6th and 12th months. Goiter recurrence was investigated by physical examination monthly, and by ultrasound in the 6th and 12th months. Students t test and Mann-Whitney test were used for statistical analysis. A p value of less than 0.05 was accepted as significant.

Results

Because of our strict exclusion criteria many of the patients who underwent thyroidectomy in our department could not be included in the study. Of 53 patients included in the study 4 (7.5%) were subsequently excluded because of follow-up problem. Surgical complications were recorded in four patients. Among them, three were temporary hypoparathyroidism which was resolved with short-course exogenous calcium replacement before discharge, and one was superior laryngeal nerve injury causing hoarseness. No recurrent laryngeal nerve injury was experienced.

A total of 40 patients have completed their six-month follow-up. TG consisted of 21 patients (20 female, 1 male; mean age: 37.1, range: 16–66, S.E.: 13.3), and CG consisted of 19 patients (16 female, 3 male; mean age: 38.1, range: 21–56, S.E.: 9.6) (p = 0.81). Ten patients in each group were also followed up for at least one year to date.

No differences were encountered between the mean FT₃ levels of the groups throughout the six-month period and at the end of first year (p = 0.36). In contrary, mean FT₄ levels of the two groups became significantly different as early as the first month (p = 0.018). This difference was maintained during the first 6 months. However, no difference was recorded at the end of the first year (p = 0.83).

The mean sTSH level of CG was found to be significantly higher than that of TG in every measurement during first six months (Fig. 1). Sixteen of 19 patients (84.2%) had an elevated sTSH level at the end of six months. By contrast, the mean sTSH level of the TG was higher than normal only on day 7. Later, this test quickly normalized by the first month, although it was never found to be lower than 1 mIU/ml. Comparing the two groups at the end of the first year, the mean sTSH level of CG (although in a decrease trend) has still been significantly higher than that of TG. When the patients in the two groups were subgrouped as elevated/normal/suppressed, there was a significant difference between CG and TG in Mann-Whitney test (p = 0.001).

Despite the fact that 8 patients (42.1%) in the CG had a FT₄ level lower than normal and 16 patients in the same group had an elevated sTSH level at the end of 6-month follow-up, only one patient developed manifest hypothyroidism (5.3%). This patient was
excluded from the study, and was put on thyroxine therapy. Among twenty patients who were followed up for one year no additional case of hypothyroidism was recorded.

No side effects of thyroxine were experienced during the early phase of the study. Ultrasound examination revealed no recurrence in 6-month and one-year controls.

Discussion

Conflicting results have been reported in studies that have researched the effects of prophylactic thyroxine after thyroidectomy for multinodular goiter. The reasons for this disagreement can be attributed to the small number of patients in some studies, the definition of recurrence, different follow-up protocols, lack of randomization, retrospective design of some studies and geographical features. In general, many researchers from non-endemic countries like Scandinavia reported no preventive effect on recurrence by thyroxine [7-10]. On the other hand, studies from endemic regions have shown that thyroxine administration have been useful. In a recent study, Miccoli and colleagues have shown that suppressive therapy with thyroxine has been effective in preventing recurrence [11]. Turkey also is an endemic goiter country and every single study which has been done in Turkey revealed that patients not given thyroxine postoperatively have developed recurrence in higher rates than that of patients who received thyroxine [4, 5, 12]. Nevertheless, no Turkish series clarified the curve of serum TSH after thyroidectomy for goiter. Although our series does not have a long follow up period yet, it has clearly shown that the difference between patients received thyroxine or not in respect to serum TSH level has been highly significant.

In an experimental study on thyroidectomized rats, Spira and coworkers showed that TSH level rose sharply following thyroidectomy and reached a maximal value within 30 days. This level was maintained for 130 days; however, there was a significant decline in plasma TSH at postoperative 180 day [13]. Unfortunately, the majority of clinical studies failed to revealed the exact course of postoperative serum TSH, probably due to high cost and other difficulties in follow up protocols. However, in the present study, we clearly observed a significant difference between the mean serum TSH levels of two groups from the first month to the first year. Moreover, the mean TSH level of the patients with no therapy is still four times that of normal. The reasons for unsuppressed mean TSH level of TG are probably due to low dosage of exogenous thyroxine and/or small thyroid remnant which is not sufficient to maintain euthyroid state. In spite of that we still advocate an 8 gram thyroid remnant in order to reduce recurrence risk. In fact, no ideal measurement technique has...
been described to evaluate the size of goiter remnant by date. However, we accept Young and McLeod’s [14] method to measure the weight of the thyroid remnant where specific gravity of thyroid tissue has a mean of 1.081, hence 1 cubic centimeter could roughly be accepted as 1 gram of thyroid tissue.

Piraneo and colleagues stated that recurrences could develop within the first two months following operation and 38% of the recurrences in their series were discovered within the first two years [1]. We did not record any recurrences within the first year of the present study in any group and this was possibly related to the extent of primary surgery.

In conclusion, both the early results of our study and the long term results of some other studies from endemic regions seem to be in favor of the use of thyroxine in the prophylaxis of recurrence after bilateral subtotal thyroidectomy for multinodular goiter at least for the first two years. Further investigations of our patients will probably give us a valuable clue for the exact duration of postoperative thyroxine administration.

References