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Prevention of Recurrences After Thyroidectomy in an Endemic Area With Prophylactic Levothyroxine Use

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Abstract: This study was planned to compare recurrence of goiters after thyroidectomy in patients who received prophylactic levothyroxine and patients who received no therapy. One hundred and twenty-six patients had been treated by bilateral subtotal thyroidectomy in the General Surgery Clinic of Karadeniz Technical University from 1987 to 1992. Eighty-eight of these patients were included in this study while the remaining patients were excluded as they were non contactable. They were divided into two groups. In group 1, there were 41 patients who had received prophylactic therapy with thyroxine 100 micro grams daily for a period of 9 to 12 months. Group 2 was composed of 47 patients without thyroxine therapy except 11

cases who had received thyroxine for 20 days or less irregularly. The mean follow-up period for all cases was 6.5 years with a range of 4 to 8 years. The results were compared using Fisher's exact test. The recurrence rates were 7.3% (3 cases) and 25.5% (12 cases) in group 1 and group 2 respectively. The difference in recurrence was found to be statistically significant ($p < 0.05$). Although the follow-up period was limited, we think routine postoperative prophylactic thyroxine therapy for 9 to 12 months in patients who have had an operation for benign nodular goiter has clinical value.

Key Words: Thyroidectomy, goiter recurrence, levothyroxine prophylaxis.

Introduction

At present, nodular goiter is the most common endocrine problem worldwide (1). In general it affects 3% to 4% of the population (2) but becomes a special health problem in endemic goiter areas, appearing in more than 10% of the population (1-3). Our hospital serves an endemic goiter area of Turkey (4).

There is still considerable controversy about the cause, optimum surgical treatment and efficacy of using exogenous thyroxine medication postoperatively in preventing recurrent goiter (5). Some recent publications have described the autonomous nature of multinodular goiter and have reported that postoperative thyroxine does not have a beneficial effect in preventing recurrent goiter (6-16). Other studies reported that not only suppressive therapy of thyroid stimulating hormone (TSH) decreases the incidence of goiter recurrences but also prophylactic thyroxine therapy for long or short periods postoperatively (3, 5, 17-25). There is no general agreement among the authors about the effectiveness of thyroxine use postoperatively in preventing recurrences.

We recommend 100 micrograms daily thyroxine therapy for prophylactic purposes for a relatively short period (9 to 12 months) postoperatively to reduce the recurrence rate.

Patients and Method

In the period from 1987 to 1992, 126 patients were operated on for benign nodular colloidal goiter and bilateral subtotal thyroidectomy in the General Surgery Clinic of Karadeniz Technical University. Among those who were prescribed prophylactic thyroxine 100 micro grams/day for 9 to 12 months, 88 were included in the study. The remaining 38 patients were excluded from the study as they were not contactable. Forty-one patients who had taken thyroxine 100 micrograms per day postoperatively for a period of 9 to 12 months were Group 1. Forty-seven patients who had not taken thyroxine or those who had taken thyroxine for a short period of 20 days or less, postoperatively (36 patients none, 11 patients 20 days or less) were Group 2. The two groups were evaluated for postoperative recurrences.

No	Age	Sex	TSH level (IU/l)	T3 level (ng/dl)	T4 level mg/dl	Time lapse (years)	Type of recurrence	Volume of recurrence (ml)
1*	20	F	1.8	152	6.5	1	nodule	45
2*	28	F	2.1	148	5.2	4	nodule	36
3*	31	F	2.4	131	8.6	8	DE	51
4	43	F	5.4	96	4.5	3	nodule	54
5	28	F	0.8	126	10.5	4	nodule	42
6	18	F	2.4	144	8.4	2	nodule	36
7	28	F	3.1	135	5.4	4	nodule	43
8	17	F	2.8	132	5.8	4	DE	55
9	19	F	1.2	110	6.8	2	DE	58
10	39	F	6.5	88	4.2	5	nodule	32
11	24	M	1.6	1.6	6.5	5	DE	74
12	32	M	3.4	112	9.4	5	nodule	46
13	23	F	3.2	113	7.4	6	nodule	57
14	30	M	2.6	140	8.8	7	nodule	37
15	24	M	3.0	104	5.8	7	nodule	43
Ave.	27		2.8	122.5	6.92	4.5		47.3

Table 1. A detailed document of the recurrence cases.

*: With thyroxine prophylaxis therapy (100 micrograms/day)

DE: Diffuse enlargement

Ave.: Average

M: Male

F: Female

During the operations the inferior thyroideal artery was not ligated routinely and about 10 to 18 g of thyroid tissue was left. The difference between the two groups was not statistically significant in term of the ages, median follow-up period, or the sexes of the patients. In all cases, bilateral subtotal thyroidectomy was performed. The mean follow-up period was 6.5 years with a range of 4 to 8 years. Physical examination was performed in all patients at least twice every year after surgery. The diagnosis of postoperative recurrence was confirmed by scintigraphic and ultrasonographic examination of the thyroid. Thyroid scintigraphy was obtained 15 minutes after an intravenous injection of 2.5 mCi of Technetium-99m pertechnetate, using a gamma camera with a pinhole collimator (Toshiba Digital Camera GCA-501S). Thereafter, the patient was examined ultrasonographically using a Shimadzu SDU-500 instrument with a 3.5MHz linear, trapezoid transducer. A sonographic pillow was used to increase the resolution. Recurrences were defined as two consecutive thyroid volumes greater than 28 ml (normal range 9 to 28 ml).

If a recurrence was diagnosed, total T3 (COAT-A count, normal range 0.4 to 4.5IU/l) levels were determined by radioimmunoassay method using a 1275 Vallac Mini Gamma Goiter instrument. Time elapse between the operation and recurrence was also recorded. The results were compared using Fisher's exact test.

Result

Eighty-eight patients with benign nodular colloid goiter were followed up evaluate postoperative recurrences. Seventeen (19.3%) were male and 71 (80.7%) were female and their ages ranged from 17 to 62 years with a mean of 31.2 years at the time of operation. Group 1 was composed of 8 (19.5%) men and 33 (80.5%) women with an age range of 17 to 59 years and a mean of 29.6 years. Group 2 composed of 9 (19.1%) men and 38 (80.9%) women with an age range of 20 to 60 years and a mean of 30.3 years.

Overall 15 (17%) recurrences were seen

postoperatively during a follow-up period ranging from 4 to 8 years (mean 6.5 years). There 7.3% recurrences occurred in group 1 patients and 12 (25.5%) recurrences occurred in group 2 patients. The difference between the two groups was statistically significant ($p < 0.05$).

The 15 patients (4 men and 11 women) with recurrence of nontoxic goiter were 17 to 43 years old (average 27 years) at the time of the thyroid resection. The mean serum T3 level in the recurrence group was 122.5 ng/dl (normal range 86-187 ng/dl) while the mean T4 level was 6.92 mg/dl (normal range 4.5-12.5 mg/dl), and the mean serum TSH level was 28 IU/l (normal range 0.4-4.5 IU/l) at the time of the recurrence. The time between the operation and the recurrence was one year in 1 case, two years in 2 cases, three years in 1 case, four years in 4 cases, five years in 3 cases, six years in 1 case, seven years in 2 cases and eight year in 1 case while the average time was 4.5 years. The recurrences were in the form of nodules in 11 patients and diffuse enlargement in the remaining 4. The volume of the goiter ranged from 32 to 74 ml (average 47 ml) (Table 1).

Discussion

There is great debate about the optimum surgical management of multinodular goiter. It is generally accepted that the pathologic process or at least a propensity towards multinodular change involves the whole gland. Different surgeons adopt different approaches usually involving radical surgical treatment to prevent recurrences. Some routinely perform bilateral subtotal thyroidectomy even if one lobe is macroscopically normal at the time of operation (5, 26, 27). One group has reported good results when performing total thyroidectomy for bilateral nodular glands (28, 29). In comparison, our approach allows for conservative initial surgical treatment and relatively short term prophylaxis with thyroxine to prevent recurrences.

It has been postulated that multinodular goiter develops as a result of TSH stimulation created by a biochemical block in the production of thyroxine in the thyroid gland (30, 31). This provides a clear rationale for the use of thyroxine in multinodular goiter and as postoperative prophylaxis. However, some researchers do not concur with this. This is because in their series of patients with multinodular goiter, the TSH level was not elevated (7, 9).

The results of many reports have shown that TSH levels are elevated after thyroid resection, probably to maintain a euthyroid state (32, 33). These findings

support the rationale of our management policy in such patients, in that after the operation, the reduction of these high TSH levels may be accomplished with prophylactic thyroxine.

In the late 1940s, postoperative thyroxine was first used for prevention of recurrent goiter. The favourable results of that study were published in 1955 (34). While some authors suggested overreplacement of thyroxine to suppress TSH (2-3 micrograms per kilogram of body weight daily) (6, 10-12, 15, 23-26, 35), other groups suggested lower dose thyroxine for prophylactic purposes (100 micrograms daily) (5, 16, 17, 22, 36). Ibis et al. (23) reported recurrence rates of 30.7%, 46% and 81.8% for patients receiving a suppressive dose of L-thyroxine, 100 microgram/day, and for those receiving no therapy respectively. It is evident in this study that although L-thyroxine in doses of 100 microgram/day is effective in preventing goiter recurrence, it gives better result in suppressive doses. We applied 100 micrograms thyroxine daily for prophylactic purposes (for 9 to 12 months postoperatively) to prevent hazardous effects of the suppressive dose of thyroxine such as subclinical hyperthyroidism in clinically euthyroid patients, and loss of bone mineral from the spine (35, 36).

How long should suppressive or prophylactic doses of thyroxine be used? The answer is not known exactly. While some authors have suggested indefinite or continuous use, (5, 6, 23-25) others propose for 6 to 18 months after the operation (10-13, 27) while still others suggest for 3 months (11, 15). We prefer prophylactic thyroxine doses for 9 to 12 months to minimize the adverse effects of the long-term therapy and to ensure patients' compliance to the regimen, owing to its short duration.

It is well documented that a second thyroidectomy is a much more hazardous procedure than the first (5, 35). Since the operative procedure does not get rid of primary pathology, recurrence of goiter is still important after thyroidectomy. Therefore, the prevention of recurrence of goiter is still a problem today. In the literature, recurrence rates vary from 5% to 30% (5, 6, 13, 14, 22, 24, 35, 37), but when data from echographic evaluations of recurrence, particularly those performed in endemic areas are considered, values around 80% are not uncommon (23-25).

We found an overall recurrence rate of 17%. In group 1 the recurrence rate was 7.3% and in group 2 it was 25.5%. The difference was statistically significant ($p < 0.05$). TSH levels in group 1 patients were found to be within normal limits at the time when recurrence was

diagnosed. In group 2, we noted 12 recurrences with slightly higher TSH levels in 2 cases while it was within the normal limits in the other 10 cases. These results suggest that there are other etiological factors (such as thyroid growth immunoglobulins) to consider for recurrences to occur in addition to high TSH levels.

We found a lower incidence of recurrence of goiter after thyroidectomy compared with the results in the literature especially from endemic goiter regions (5, 6, 13, 14, 22-25, 30). The length of the follow up is a major determinant of the recurrence rate. The reported postoperative follow-up period was much longer than in our study. Those studies with longer follow-up periods gave higher recurrence rates when compared to our overall recurrence rate (23-25). The method of diagnosing the recurrence is another important factor in determining the recurrence rate. On physical examination, the recurrence can only be diagnosed in 71.2% of cases. But by the scintigraphic and ultrasonographic examination of the thyroid the recurrence rate rises to 80.6% and 96.4% respectively (23). We performed scintigraphic and ultrasonographic examination only in those patients suspected of having recurrence upon physical examination. In addition, according to some authors recurrence was defined as two consecutive thyroid volumes greater than 28 ml (normal range 9 to 28 ml), or since some patients had a thyroid volume of 28 ml or greater after thyroidectomy, as two consecutive

volumes greater than the initial volume (15). Others set the criteria to define the recurrence of nodular lesions in the residual thyroid tissue as follows: (a) presence of a hypoechoic or hyperechoic nodular pattern with a maximum diameter longer than 5 mm; (b) identification of a perinodular hypoechoic or hyperechoic halo; and (c) description of an anechoic lesion with a reinforced posterior wall (24). We used the criteria that define the recurrences on thyroid volume basis which is less sensitive than the others. There might be other reasons for our lower overall recurrence rate.

Although the overall recurrence rate in our study is lower when compared with the values in due to the above-mentioned possible reasons, the difference between thyroxine treated and untreated groups is still statistically significant. We think that the choice of 100 micrograms a day of thyroxine for a period of 9 to 12 months is appropriate. All patients receiving this dose are less likely to have recurrences. Conservative surgical treatment plus postoperative prophylactic thyroxine therapy for 9 to 12 months decreases recurrence of multinodular goiter at least during the early follow-up period.

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