PAPERS AND SHORT REPORTS

Does prophylactic thyroxine treatment after operation for non-toxic goitre influence thyroid size?

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Abstract

In order to evaluate the influence of thyroxine treatment on thyroid volume after thyroidectomy for non-toxic goitre 110 consecutive patients were randomised to receive thyroxine (150 μg daily) or no treatment three months after operation.

Thyroid volume determined by ultrasonography did not differ significantly between the two groups one year after operation. Nevertheless, a similar decrease in volume was seen from three to 12 months postoperatively in the thyroxine treated and no treatment groups (median 18 (range 8-70) ml to 16 (range 7-57) ml, and median 20 (range 9-72) ml to 17 (range 8-58) ml, respectively). Three patients (two given thyroxine) had recurrence of goitre within the observation period of one year.

In this series thyroid volume decreased during the first postoperative year independently of thyroxine treatment. Hence it seems questionable whether postoperative thyroid function studies can identify patients at risk of recurrence of goitre after operation for non-toxic goitre and whether routine postoperative treatment with thyroxine is justifiable.

Introduction

Levothyroxine (thyroxine sodium) in doses of 150-200 μg daily is frequently recommended to prevent regenerative hyperplasia and further goitrogenesis after subtotal thyroidectomy for non-toxic goitre.[1] It is well known that thyroxine as well as triiodothyronine given to patients with diffuse non-toxic goitre suppresses thyroid volume by some 20-30%.[2,3] No such data are, however, available regarding the effect on other types of goitre or after thyroidectomy. Though the plasma thyroid stimulating hormone concentration is generally not raised in patients with non-specific goitre,[4-8] prophylactic treatment should theoretically be useful, as suppressing thyroid stimulating hormone is believed to hinder goitrogenesis.

Reports on recurrence of goitre after thyroid resection are sparse,[9-12] and recently the influence of thyroxine given as prophylaxis has been questioned.[13] Other studies have had various shortcomings: they have been retrospective and non-randomised; follow up has been sporadic; and evaluation of the recurrence of goitre (by thyroid size or volume) has been performed by different clinicians using inaccurate methods—for example, palpation and scintiscan.

This study aimed at investigating thyroid volume (measured by ultrasonography[14]) and thyroid function in a consecutive group of patients operated on for non-toxic goitre and randomised postoperatively to thyroxine treatment or no treatment.

Patients and methods

Three months after operation for non-toxic goitre 110 consecutive patients were allocated by random numbers[15] to receive 150 μg thyroxine daily or no treatment. An interval of three months was chosen because it allowed precise ultrasound evaluation of thyroid size not possible in the immediate postoperative period. Six and 12 months after operation thyroid volume and thyroid function were re-evaluated. Only a low degree of blindness could be achieved—that is, only the investigators performing the ultrasound scans were unaware of the study group to which patients had been allocated. All patients gave informed consent to the study. Five of the 52 patients randomised to receive thyroxine and three of the 58 randomised to no treatment had had a previous thyroidectomy. Table I summarises the clinical details of patients in the two groups.

In a large non-goitrous group of healthy subjects we found that the thyroid volume ranged from roughly 9 to 28 ml (mean 18·6 (SD 4·5) ml).[14] We therefore defined recurrence of goitre as two consecutive measured volumes greater than 28 ml or, since 13 patients (six randomised to receive thyroxine) had a thyroid volume of 28 ml or greater after thyroidectomy, as two consecutive volumes greater than the initial volume.

Serum thyroxine, triiodothyronine, and thyroid stimulating hormone

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TABLE I—*Postoperative data in 110 patients with non-toxic goitre subsequently randomised to thyroxine or no treatment. (Median values expressed with ranges in parentheses)*

Variable	Thyroxine treatment	No treatment
No of patients	52	58
Unilateral resection	29	35
Bilateral resection	23	23
Male/female patients	6/46	6/52
Age (years)	40 (15-63)	40 (19-65)
Weight of removed tissue (g)	40 (6-178)	45 (6-218)
Thyroid volume (ml)	18 (8-70)	20 (9-72)
Thyroid stimulating hormone (mU/l)	1·7 (0·2-22·0)	2·0 (0·2-22·0)
Thyroxine (nmol/l)	94 (62-129)	92 (62-160)
Triiodothyronine (nmol/l)	2·0 (1·4-3·5)	2·0 (1·3-3·8)
Preoperative diagnosis:		
Multinodular goitre	21	21
Solitary cold nodule	22	28
Diffuse goitre	3	3
Cyst	6	6

TABLE II—*Postoperative data in 110 consecutive patients with non-toxic goitre in relation to type of operation. (Median values expressed with ranges in parentheses)*

Variable	Unilateral resection	Bilateral resection
No of patients	64	46
Age (years)	40 (19-65)	39 (15-60)
Weight of removed tissue (g)	34 (6-166)	62** (11-218)
Thyroid volume (ml)	20 (8-70)	15* (8-72)
Thyroid stimulating hormone (mU/l)	1·7 (0·2-22·0)	3·0* (0·2-8·9)
Thyroxine (nmol/l)	98 (69-160)	92* (62-131)
Triiodothyronine (nmol/l)	2·0 (1·5-3·8)	2·0 (1·3-2·7)

* $p<0·05$, ** $p<0·01$.

18 ml (8-70 ml) three months after thyroidectomy to 16 ml (7-57 ml) at 12 months ($p<0·01$). A similar decrease in volume was seen in the group not given thyroxine—that is, from 20 (9-72) ml at three months to 17 (8-58) ml at 12 months ($p<0·01$; table III).

A significant decrease in serum thyroid stimulating hormone and increase in serum thyroxine concentrations were found in the thyroxine treated patients, whereas these values were unchanged in the no treatment group. Serum triiodothyronine concentrations were unaltered in both groups (table III).

Three months after operation 14 patients subsequently randomised to no treatment had a raised serum thyroid stimulating hormone concentration (>3·3 mU/l). The median concentration in these patients was 5·4 mU/l (3·5-22·0 mU/l), and their median thyroid volume decreased from 17 (9-36) ml at three months to a median of 14 (9-29) ml 12 months postoperatively ($p<0·02$).

Three patients had recurrence of goitre within the observation period. Two of these were given thyroxine postoperatively, had unilateral resections, and had normal serum thyroid stimulating hormone concentrations postoperatively (0·4 and 0·7 mU/l). Their thyroid volumes at three, six, and 12 months were 29, 45, and 35 ml and 30, 51, and 57 ml, respectively. The other patient was not given thyroxine; she also had a unilateral resection and a normal serum thyroid stimulating hormone concentration postoperatively (2·7 mU/l), and her thyroid volumes were 23, 30, and 32 ml.

All 110 patients were followed up for one year after thyroidectomy, and there were no drop outs. Owing to symptoms of hyperthyroidism (tachycardia, weight loss, diarrhoea or loose stools, sweating, or nervousness) 14 of the 52 patients (27%) given thyroxine had their dose reduced to 100 μg daily. There were no other side effects of thyroxine.

Discussion

This study found no significant difference in thyroid volume between the two groups one year after operation for non-toxic goitre. In addition, a similar decrease in thyroid volume from the third to 12th months was shown whether thyroxine was given or not. Furthermore, patients with raised serum thyroid stimulating hormone values three months after operation and not randomised to thyroxine treatment had a significant fall in thyroid volume during the observation period. These findings and the fact that two of the three patients with recurrence of goitre received thyroxine postoperatively question whether routine thyroxine is justifiable and whether standard thyroid function variables can identify those patients at risk of recurrence.

Generally thyroid size is judged clinically by palpation, which is inexact and irreproducible.[16] In addition to a precise evaluation of thyroid size in our study, we defined recurrence using an objective measurement that avoided the confounding effect of a group of patients having enlarged thyroid glands postoperatively. Our results cannot be explained by differences between the two groups, as all the pretreatment data after operation were similar.

Despite the lack of controlled studies it has generally been recommended that these patients should be treated postoperatively

TABLE III—*Serum thyroxine, triiodothyronine, and thyroid stimulating hormone concentrations and thyroid volumes in 110 consecutive patients three, six, and 12 months after operation for non-toxic goitre. Values expressed as median (range), and [95% confidence interval]*

	3 Months	6 Months	12 Months	p Value 3-12 months
Thyroid volume (ml):				
Thyroxine treatment	18 (8-70) [15 to 21]	16 (8-55) [14 to 18]	16 (7-57) [13 to 17]	$p<0·01$
p Value	NS	NS	NS	
No treatment	20 (9-72) [16 to 22]	18 (8-52) [16 to 19]	17 (8-58) [15 to 19]	$p<0·01$
Thyroid stimulating hormone (mU/l):				
Thyroxine treatment	1·7 (0·2-22·0) [1·2 to 2·9]	0·7 (0·2-3·8) [0·4 to 1·1]	0·9 (0·2-3·8) [0·3 to 2·0]	$p<0·001$
p Value	NS	$p<0·001$	$p<0·001$	
No treatment	2·0 (0·2-22·0) [1·9 to 2·6]	1·8 (0·2-12·0) [1·5 to 2·2]	2·1 (0·5-13·5) [1·6 to 2·5]	NS
Thyroxine (nmol/l):				
Thyroxine treatment	94 (62-129) [89 to 100]	128 (73-209) [121 to 141]	123 (74-190) (117 to 129)	$p<0·001$
p Value	NS	$p<0·001$	$p<0·001$	
No treatment	92 (62-160) [84 to 100]	96 (58-147) [89 to 102]	95 (62-150) [90 to 101]	NS
Triiodothyronine (nmol/l):				
Thyroxine treatment	2·0 (1·4-3·5) [1·9 to 2·2]	2·0 (1·3-3·0) [1·8 to 2·2]	2·0 (1·3-2·8) [1·8 to 2·1]	NS
p Value	NS	NS	NS	
No treatment	2·0 (1·3-3·8) [1·9 to 2·1]	1·9 (1·3-3·2) [1·8 to 2·0]	2·0 (1·5-3·4) [1·9 to 2·2]	NS

concentrations were determined as described.[14] Ultrasonography and calculation of the total thyroid volume were performed with compound scanners (types 3401 and 1846, Brüel and Kjær, Nærum, Denmark).[14] Accuracy and precision of the method have been reported.[14] The mean coefficient of variation of two determinations in this range of thyroid volumes generally lies between 4% and 8%.

Statistics.—Results are expressed as medians and ranges. Unpaired data were compared by the Mann-Whitney U test and paired data by the Wilcoxon test. Probability values <0·05 were regarded as significant.

Results

Postoperative pretreatment data in the two groups were similar (table I). Patients with bilateral resections had significantly more thyroid tissue removed and at three months postoperatively had significantly higher serum thyroid stimulating hormone concentrations, lower serum thyroxine concentrations, and smaller thyroid volumes than patients with unilateral resections (table II).

In the thyroxine treated group the median thyroid volume decreased from

with thyroxine in order to avoid recurrence.[1] The basis for this lies in the concept that increased concentrations of thyroid stimulating hormone are the main causal factor in the development and recurrence of non-toxic goitre. Hence it has been shown that both thyroxine and triiodothyronine treatment reduce thyroid volume in patients with diffuse goitre and that withdrawal is followed by subsequent regrowth.[2,3] This volume reducing effect, however, has been recorded only in patients with diffuse goitre, and only a minority of patients operated on for non-toxic goitre (six of the 110 in this study) had a diffuse enlargement of the thyroid. Furthermore, finding serum thyroid stimulating hormone concentrations within the normal range in patients with longstanding goitre[4-8] and recurrent non-toxic goitre[8] casts doubt on the role of thyroid stimulating hormone in the genesis of goitre in man, though concentrations of the hormone may be raised in the early phase of goitre development.[5,17]

Hemithyroidectomy in rats was followed by hypertrophy of the remaining lobe[18,19] associated with increased serum thyroid stimulating hormone concentrations.[18] Clark *et al*, however, did not find basal concentrations of the hormone to be above normal in patients who had had hemithyroidectomy for unilateral lesions.[19] In accordance with this, Matte *et al* found a significant decrease in serum thyroxine and increase in serum thyroid stimulating hormone concentrations and an exaggerated response of thyroid stimulating hormone to the releasing factor after hemithyroidectomy in euthyroid patients, but all changes occurred within the normal range and were transient.[20] This may possibly explain why our study did not show significant changes in serum thyroxine and thyroid stimulating hormone concentrations in the patients not randomised to thyroxine after thyroidectomy, as these variables were not examined until three months postoperatively. We have no explanation for the decrease in thyroid volume from the third to 12th months in the group not given thyroxine, though conceivably serum thyroxine was decreased and serum thyroid stimulating hormone increased in the three months after operation, leading to compensatory hypertrophy of the thyroid. We have no data on changes in thyroid volume between the immediate postoperative period and the first three months. The very variable amounts of thyroid tissue left after thyroidectomy made it impossible to evaluate and compare this value with the one obtained by ultrasonography after three months.

Studies in snell dwarf mice lacking thyroid stimulating hormone have shown compensatory thyroid hyperplasia after hemithyroidectomy.[21] Furthermore, studies in patients have shown no correlation between the rate of goitre enlargement and serum thyroid stimulating hormone concentrations,[22] suggesting that the regulation of thyroid growth in at least some conditions may be independent of the hormone.

Recent studies employing four separate methods have found circulating autoantibodies capable of stimulating thyroid growth selectively (thyroid growth stimulating immunoglobulins) in serum samples from patients with goitrous hyperthyroid Graves' disease.[23-26] These autoantibodies have also been detected in the serum of patients with non-toxic goitre.[23,26] Van der Gaag *et al* found that values for thyroid growth stimulating immunoglobulins in euthyroid subjects tended to be high in diffuse goitre, nodular goitre recurring after partial thyroidectomy, and goitre with recent growth.[27] A positive correlation between thyroid volume and thyroid growth stimulating immunoglobulins[28] lends further support to the possibility of an immunological explanation for goitre formation. These results also show the complexity of the pathogenesis of goitre and underline the possibility suggested by Studer *et al* of large variations in the individual response to a goitrogen.[29]

In conclusion, thyroid volume decreased during the first year after thyroidectomy for non-toxic goitre independently of thyroxine treatment. It therefore seems questionable whether postoperative thyroid function studies can identify patients at risk of recurrence of goitre and whether routine postoperative treatment with thyroxine is justifiable at all. Only further follow up of larger groups of patients will clarify whether the long term recurrence rate is influenced by postoperative thyroxine treatment.

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