

## Rapid preoperative blockage of thyroid hormone production / secretion in patients with Graves' disease

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### Summary

**PRINCIPLES:** Preoperative management of hyperthyroid patients with Graves' disease who are unable to tolerate thionamides or have poor adherence to therapy is a challenging clinical problem. The goal of our study was to demonstrate the clinical efficacy of a rapid preoperative thyroid hormone blocking protocol and to assess specific surgical and treatment-related complications.

**METHODS:** Ten patients with thyrotoxicosis due to Graves' disease were treated with a rapid thyroid hormone blocking protocol of Lugol's solution, dexamethasone and a beta-blocker. Two patients continued to receive antithyroid therapy with carbimazole. Adrenal function was assessed 4–6 weeks postoperatively with a low dose (1 µg) adrenocorticotrophic hormone-stimulation test.

**RESULTS:** Before treatment, all patients had severe hyperthyroidism. Baseline median and interquartile range (IQR) of fT4 was 68.9 (45.7–92.1) pmol/l, and baseline median fT3 and IQR, 30 (19.1–40.9) pmol/l.

After 10 days of treatment, the levels of free hormones were significantly reduced with fT4 concentrations slightly elevated (fT4, 26.7 [17–36.4] pmol/l,  $p < 0.001$  compared with corresponding pretreatment values), and the fT3 concentration was normal in 8/10 patients (fT3, 6.1 [4.6–7.6] pmol/l,  $p < 0.001$  compared with corresponding pretreatment values).

All patients were clinically euthyroid with a heart rate of  $< 80$ /min. Drug tolerability was excellent, and there were no side effects or exacerbation of hyperthyroidism. The peri- and postoperative course was uneventful in all cases. Adrenal function was normal in 7 out of 10 patients 4–6 weeks postoperatively. Three patients showed prolonged secondary adrenal insufficiency with normalisation of adrenal function after 3 to 6 months.

**CONCLUSION:** Rapid and effective preoperative preparation of patients with Graves' disease is achievable with Lugol's solution, dexamethasone and a beta-blocker. The risk of temporary hypothalamic-pituitary-adrenal axis suppression has to be taken into account.

**Key words:** preoperative preparation; Graves' disease; iodine; Lugol's solution; dexamethasone

### Introduction

Graves' disease is the most common cause of hyperthyroidism. Although antithyroid drugs and radioactive iodine are favoured treatment options [1], total thyroidectomy is the therapy of choice for a subset of patients. Apart from individual preference, this subset of patients includes those with large and compressive goitres, those who fail to respond to antithyroid drugs, those with moderate-to-severe endocrine orbitopathy or nodules suspicious for thyroid cancer, and pregnant women [2]. When performed by a skilled surgeon, total thyroidectomy is a safe procedure with a very low risk of complications [3] and rate of recurrence. However, it is important that in patients with Graves' disease selected for thyroidectomy, thyroid function should be adequately controlled before surgical intervention.

Thyroid storm is a rare but severe complication of thyrotoxicosis with a high rate of mortality and deleterious effects on the cardiovascular system. It may occur in patients with uncontrolled hyperthyroidism who undergo non-thyroid or thyroid surgery. Thus, the goal of preoperative regimens is to restore euthyroid function and homeostasis by decreasing thyroid hormone synthesis and secretion, and to control the peripheral actions of thyroid hormones.

Presently, patients with Graves' disease are usually prescribed thionamides (methimazole or carbimazole), beta-blockers and iodine in the form of Lugol's solution preoperatively [4]. Thionamides block the synthesis of thyroid hormones and normalise hormone levels within weeks. Thionamide use is restricted or contraindicated in those with side effects (rash, arthralgia, hepatopathy or agranulocytosis), those who fail to adhere to therapy or those who require rapid normalisation of thyrotoxicosis. Therefore, alternative thionamide-free regimens for controlling hyperthyroidism and a rapid thyroid hormone blocking protocol have been studied extensively in patients with Graves' disease [5–7] or as preparation before thyroidectomy [8–12]. Most rapid thyroid hormone blocking protocols are based on multimodal approaches that target thyroid hormone synthesis and secretion (iodine containing preparations, i.e. iodinated oral cholecystographic agents [OCAs]), inhibit peripheral conversion to T3 (glucocorticoids, OCAs), and

attenuate the peripheral action of thyroid hormones on adrenergic receptors (beta-blockers).

Iodine is the oldest thyrostatic agent, and its use in patients with Graves' disease was first described by Plummer in the early 1920s [13]. Iodine decreases blood flow and thyroid vascularity [14–16]. Although some studies suggest a positive effect of preoperative Lugol's solution on reduction of intraoperative blood loss [16], others do not [17]. However, current guidelines suggest adding iodine to the immediate preoperative preparation of patients with Graves' disease [4].

Iodine in supraphysiological doses inhibits thyroid hormone synthesis (defined as the Wolff-Chaikoff effect) [18] and reduces hormone release into the circulation [19]. However, the Wolff-Chaikoff effect is temporary and an escape phenomenon is common [20] (i.e., the effect of treatment with iodine lasts for only 10–14 days). In addition, the clearance of iodine by the thyroid gland of patients with hyperthyroidism is altered and aggravation of hyperthyroidism after iodine is possible (defined as the Jod-Basedow effect) [21]. Therefore, iodine should only be administered to thionamide-pretreated patients.

Different preparations containing iodine exist (table 1). In the past, OCAs were often used in hyperthyroid patients because they also inhibited 5'-deiodinases [22], leading to a rapid reduction of circulating T3 levels [9] and to a rise of the reverse T3 concentration. However, tyropanoate and sodium ipodate were withdrawn from the drug market, and the availability of iopanoic acid is restricted.

The goals of our study, treating patients with severe Graves' disease with a rapid preoperative thyroid hormone blocking protocol of Lugol's solution, dexamethasone and a beta-blocker, were as follows:

- to demonstrate the clinical efficacy in terms of achieving rapid (i.e. within days), biochemical (i.e. normalisation of free thyroid hormone [fT4 and fT3] values) and clinical (i.e. heart rate) euthyroidism.
- to investigate the effect of iodine in this setting in patients without concomitant thionamide therapy.
- to assess specific surgical (i.e. hypoparathyroidism, blood loss) and treatment-related complications (i.e. suppression of hypothalamic-pituitary-adrenal [HPA]-axis).

## Subjects and methods

Ten patients with severe thyrotoxicosis due to Graves' disease who were scheduled for total thyroidectomy were included in this study. The indications for thyroidectomy were: poor adherence to or severe side effects from thionamide therapy, and at least one of the following criteria: patient's preference, the presence of moderate-to-severe orbitopathy, and/or a large and compressive goitre. Patients

were treated with a rapid preoperative thyroid hormone blocking regimen (see protocol below). Thyroid function was assessed by measuring fT4 and fT3. All hormones (fT4, fT3 and cortisol) were quantified with competitive electrochemiluminescence immunoassays (ECLIA, Cobas® 6000 analyser, Roche Diagnostics; reference ranges for fT4 and fT3 were 12–22 pmol/l and 3.1–6.8 pmol/l, respectively). Eight patients were admitted to our hospital to ensure compliance with the multiple dosing treatment regimen and for close monitoring in severe hyperthyroid patients, and two patients were treated in an ambulatory setting. Decision if hospitalisation was necessary was made on an individual basis. Surgery was performed 10 days after starting treatment in 8/10 patients. In 2 patients thyroidectomy was done 14 days after initiation of the blocking regimen. All total thyroidectomies were performed by a single surgeon (WM). T4 substitution with levothyroxine was initiated after thyroidectomy.

### Rapid preoperative thyroid hormone blocking protocol

All patients gave informed consent and were treated with 5% Lugol's solution (3 × 13 drops/d, equivalent to approximately 3 × 81.25 mg iodine), 2 mg/d dexamethasone (2 × 1 mg/d) and a beta-blocker (propranolol, metoprolol or bisoprolol). The dose of the beta-blocker was titrated to a target heart rate of <80/min. In two patients who failed to adhere to antithyroid therapy, carbimazole treatment was continued until surgery. Dexamethasone was terminated a few days after surgery, and all patients received hydrocortisone (30 mg/d). Adrenal function was assessed post-operatively at 4–6 weeks with a 1 µg adrenocorticotrophic hormone (ACTH) stimulation test. Patients skipped their recommended hydrocortisone dose at least 24 h before testing. A stimulated (peak) cortisol level of ≥500 nmol/l was indicative of normal adrenocortical function, at which time hydrocortisone treatment was terminated.

### Statistical analysis

Data are reported as medians with interquartile range (IQR). Median values were compared with corresponding baseline values by the Student's t-test. A p < 0.05 was considered significant.

## Results

Ten patients (seven females and three males; mean age 35 years; range 21–50 years) were included. Eight patients had experienced severe side effects to thionamide therapy (table 2), and two patients had poor adherence to thyrostatic treatment and developed uncontrolled hyperthyroidism. Hyperthyroidism was severe in all cases, with baseline median and IQR fT4, 68.9 (45.7–92.1) pmol/l and baseline median fT3 30 (19.1–40.9) pmol/l.

**Table 1:** An overview of oral iodine-containing preparations administered preoperatively to patients with Graves' disease.

Preparation	Composition	Usual daily dose	References
Lugol's solution	5–8 mg iodine/drop	3 × 5–10 drops	[4, 16]
Saturated solution of potassium iodide (SSKI)	30–50 mg iodine/drop	3 × 1–4 drops	[6, 7]
Potassium iodide (KI), eg. in Switzerland "Kaliumiodid AAPot 65 mg <sup>®n</sup> "	50 mg iodine/tab. l.	3 × 1 tab. l.	[10]
Iopanoic acid	66.7% organic-bound iodine	2–4 × 500 mg	[8, 11, 22]

Most patients had diffuse goitres (mean volume measured by ultrasound 27.8 ml, range 13–70 ml; and mean weight on pathological examination 40.3 g, range 22–78 g). Drug tolerability was excellent, and there were no side effects such as exacerbation of hyperthyroidism or glucocorticoid-associated complications (e.g., hyperglycaemia).

After 10 days of treatment, the levels of free hormones were significantly reduced, with fT4 concentrations slightly elevated (fT4 26.7 [17–36.4] pmol/l,  $p < 0.001$  compared with corresponding pretreatment values), and the fT3 concentration normal in 8/10 patients (fT3, 6.1 [4.6–7.6] pmol/l,  $p < 0.001$  compared with corresponding pretreatment values) (fig. 1a/1b). Two patients (numbers 1 and 4) were treated for 14 days and had complete normalisation of fT3.

Before surgery all patients were clinically euthyroid with a heart rate of  $< 80$ /min. There was no complication during surgery, and there was only minimal blood loss ( $< 50$  ml) in all patients. There was no reported case of severe bleeding, hypoparathyroidism or vocal cord dysfunction. A postoperative ACTH stimulation test was normal in seven patients; however, three patients showed prolonged secondary adrenal insufficiency with normalisation of adrenal function after 3 to 6 months.

## Discussion

We demonstrate that combined therapy with Lugol's solution, dexamethasone and a beta-blocker is a very effective and rapid-onset regimen to prepare patients with severe Graves' disease for surgery, even in an outpatient setting.

Within 10 days of treatment, all patients were clinically euthyroid and normalisation of fT3 was achieved in almost all patients.

Managing hyperthyroid patients with severe Graves' disease who are unable to tolerate thionamides or to adhere to therapy is a challenging problem, albeit quite rare in daily clinical practice. Apart from the above mentioned approaches, the use of lithium [23] or plasmapheresis [24] has also been advocated. Lithium inhibits thyroid hormone release into the circulation, but has a narrow therapeutic range and there is a risk of toxicity. Plasmapheresis requires trained medical staff, is invasive and is associated with the risk of serious complications [25]. Based on our experience, plasmapheresis should be reserved for refractory or emergency cases.

There are several differences in the mechanisms of action between OCA and iodine/iodide in the form of saturated solution of potassium iodide (SSKI), potassium iodide or Lugol's solution. OCA resulted in a more pronounced decrease of the T3 level and heart rate, but discontinuing treatment is associated with a rebound of thyroid hormone secretion and a rise of T3 and T4 concentrations [6, 7]. Compared with SSKI, potassium iodide and Lugol's solution, the decrease in the T4 level is less pronounced with OCAs, which can be explained by the inhibition of conversion from T4 to T3 and reduction of the T4 flux from the plasma to the liver by these agents [26].

Thyroid hormones facilitate the action of catecholamines, presumably by altering the affinity and number of adrenergic receptors or by modifying postreceptor mechanisms [27]. Beta-blockers are often used effectively to treat in-

**Table 2:** Patient characteristics.

Patient number	Age	Sex	Indication / adverse event on thionamide	Thyroid volume (ml) <sup>1</sup>	Thyroid weight (g) <sup>2</sup>	Thionamide / daily dose (mg) <sup>3</sup>	Beta-blocker / daily dose (mg) <sup>4</sup>	fT4 (pmol/l)		fT3 (pmol/l)		Duration of thionamide therapy (weeks)	Interval between stopping thionamide and blocking Tx (days)
								Before treatment	After treatment <sup>5</sup>	Before treatment	After treatment <sup>5</sup>		
1	36	M	Agranulocytosis	70	78	—	Propranolol / 320	100.0	28.8	35.0	4.7	0 <sup>6</sup>	N.A. <sup>6</sup>
2	38	F	Agranulocytosis	16	22	—	Metoprolol / 250	61.3	29.7	30.0	8.7	10	14
3	34	F	Malcompliance	60	78	Carbimazole / 45	Metoprolol / 200	100.0	23.2	50.0	6.8	2	N.A.
4	32	F	Generalised exanthema	18	25	—	Propranolol / 160	77.3	19.1	34.0	4.4	8	60
5	26	F	Hepatopathy	14	41	—	Metoprolol / 200	49.5	24.0	21.0	5.4	72	28
6	50	F	Malcompliance	13	29	Carbimazole / 45	Bisoprolol / 10	55.8	20.9	31.0	5.4	20	N.A.
7	46	M	Vasculitis	16	30	—	Bisoprolol / 5	46.9	33.4	15.0	6.4	0 <sup>6</sup>	N.A. <sup>6</sup>
8	32	M	Arthritis	23	41	—	Propranolol / 160	54.5	19.1	27.0	3.6	6	20
9	35	F	Thrombopenia	N/A	33	—	Metoprolol / 100	100.0	16.4	41.0	6.5	4	7
10	21	F	Arthralgia, pruritus	20	26	—	Metoprolol / 150	44.6	19.5	16.0	3.8	6	7

<sup>1</sup> Determined by ultrasound (volume calculated with B-mode standard ultrasonography)

<sup>2</sup> On pathological examination after total thyroidectomy

<sup>3</sup> Carbimazole treatment was continued only in patients with poor compliance

<sup>4</sup> Beta-blocker dose was titrated to a resting heart rate of  $< 80$ /min.

<sup>5</sup> After 10 or 14 days (Patients 1 and 4) treatment with the blocking regimen

<sup>6</sup> Owing to complications in the past, thionamide therapy was not restarted in these patients

NA = not available, not applicable

dividuals with hyperthyroidism, and they should be prescribed for all symptomatic patients if no contraindications are present. It should also be noted that clearance of beta-blockers in hyperthyroid states is accelerated [28]. In fact, several patients in our study required a very high dose of beta-blocker to control the heart rate. Due to the longer half-life of T4, the beta-blocker dose should be tapered off over the course of several days after thyroidectomy.

Glucocorticoids inhibit the conversion from T4 to T3, they have direct inhibitory effects on hormone secretion [29] and promote vasomotor stability. They are routinely given during thyroid storm [30]. Moreover, long-standing or severe thyrotoxicosis is associated with an impaired adrenocortical reserve [31]. In this study, dexamethasone was given twice daily at 2 mg/day for 10–14 days (including the postoperative period), which is similar to a previously published regimen [11]. Thus, development of secondary adrenal insufficiency is possible.

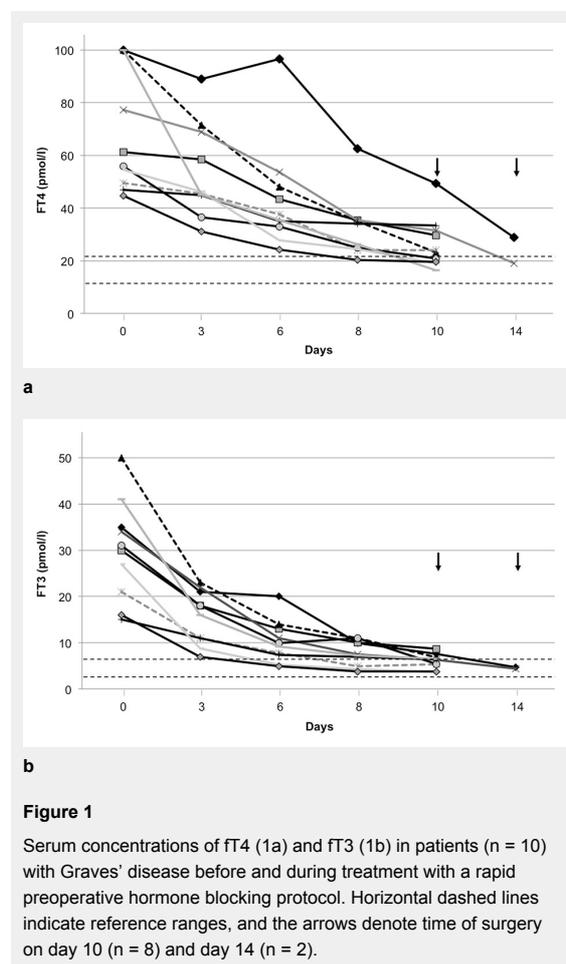
To the best of our knowledge, this is the first series of patients with severe Graves' disease to be treated with Lugol's solution, dexamethasone and a beta-blocker for the purpose of blocking thyroid hormone function before total thyroidectomy. Table 3 provides an overview of previous reports with different, alternate or preoperative blocking regimens in patients with Graves' disease. Compared to other authors [8–12] who used mainly iopanoic acid, we studied the use of iodine in the form of Lugol's solution, use and availability of which is not restricted. In our study only 2/10 patients (20%) had concomitant treatment with anti-

thyroid drugs, which is a considerably lower rate than in other reports (71% in [12] and 82% in [11]).

In contrast to other studies [8–12], we measured fT3 and fT4, which represent important criteria to define biochemical euthyroidism. Liel [32] showed in athyreotic patients who withdrew from levothyroxine treatment that the mean half-life ( $t_{1/2}$ ) of fT3 (15.5 d) and fT4 (11 d) was significantly longer than the  $t_{1/2}$  of the corresponding total hormones (TT4: 7 d; TT3: 0.8 d, respectively). The difference was caused by the continuous release of T4 from binding proteins and the ongoing conversion of T4 to T3 in the peripheral tissues. Thus, defining biochemical euthyroidism on the ground of normal TT4 and TT3 levels only can be misleading in these situations. One can speculate that – even in presence of normalised TT4 and TT3 values – there is still a significant amount of thyroid hormones in the circulation, which exposes the patient to risk. Even more important is the fact that absolute total hormone concentrations are influenced by the levels of their corresponding binding proteins such as thyroxin-binding globulin (TBG) which itself is altered in several situations. As an example TBG levels are reduced in acute illness [33] and TBG metabolism is enhanced by hyperthyroidism [34], leading to false low TT4 and TT3 measurements and therefore putting the reliability of these values in the above-mentioned situations into question.

In our series and in accordance with previous studies we report no peri- and postoperative surgical complications such as haemorrhage, vocal cord paralysis or hypoparathyroidism, and the postoperative course was uneventful in all cases. Of particular importance is the observation that the administration of iodine to eight patients without concomitant thionamide therapy did not result in an aggravation of hyperthyroidism or even thyroid storm within a time period of 10–14 days.

Assessment of adrenocortical function was normal in seven out of ten patients at 4–6 weeks after intervention; however, three patients experienced prolonged suppression of the hypothalamus-pituitary-adrenal-axis. Two patients (Nrs 8 and 10) demonstrated subnormal response in the low-dose ACTH test (peak cortisol 321 nmol/l and 460 nmol/l, respectively) but a normalisation of HPA-function within 3 months. One patient (Nr 1) with long-standing Graves' disease and severe agranulocytosis had a prolonged course with complete recovery of adrenocortical function after 6 months. Thus, it can be hypothesised that in this case the long-standing hyperthyroidism *per se* was a co-factor for HPA-axis suppression as described in the literature [31]. Compared with previous studies we used lower [5, 29] or equivalent doses [8, 11] of glucocorticoids. To our knowledge no study with lower glucocorticoid doses exists and the risk of side effects and the therapeutic effect (i.e. adequate inhibition of conversion to T3) needs to be carefully balanced. Adrenocortical function was not tested in the other studies using glucocorticoids [5, 8, 11] and a direct comparison regarding this complication is therefore not possible. In our opinion, the risk of about 30% of developing a probably self-limiting suppression of HPA function by far outweighs the risk of uncontrolled hyperthyroidism or thyroid-storm in a surgical setting. However,



we recommend adequate testing of cortisol secretion after treatment with our blocking regimen.

Our case series has limitations. We intended to treat these patients with a quite rare clinical condition in accordance with our best knowledge and based on the literature, which is characterised by the scarcity and considerable heterogeneity of the data and a complete absence of controlled studies. Therefore, no adequate comparison with a standardised treatment protocol was readily available. As in other studies our number of treated patients is small and some of the patients were concomitantly treated with thyrostatic drugs what may limit to a certain point the conclusions that can be drawn from this work. With regard to the definitive assessment of the safety and tolerability of the applied treatment regimen further studies with larger patient numbers are needed.

## Conclusion

In conclusion, our report shows that effective and rapid preoperative preparation of patients with Graves' disease is achievable with a treatment regimen of Lugol's solution, dexamethasone and beta-blockers.

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**Table 3:** An overview over previous reports of different blocking regimens.

1st author Reference number	Year	n	Treatment protocol	Duration (days)	TT4 pre/post (nmol/l; mean $\pm$ SD/SE)	TT3 pre/post (nmol/l; mean $\pm$ SD/SE)	nTT4 (n)	nTT3 (n)
<i>Alternate thyrostatic regimens in patients with Graves' disease (no preoperative preparation regimens)</i>								
Arteaga [5]	1983	18	DEX 5 mg q12h sc (n = 6) IOP 3g q24h po (n = 6) IOP 3g q24h po and DEX 5 mg q12h sc (n = 6)	1	253.5 $\pm$ 10.1 / 265.1 $\pm$ 21.9 224.0 $\pm$ 15.4 / 236.8 $\pm$ 20.6 232.9 $\pm$ 11.6 / 239.4 $\pm$ 5.1	9.5 $\pm$ 1.9 / 6.9* $\pm$ 1.4 6.7 $\pm$ 0.8 / 4.3* $\pm$ 0.5 9.1 $\pm$ 2.0 / 3.0* $\pm$ 0.4	0/18	1/6 1/6 4/6
Arteaga [5]	1983	6	IOP 500 mg q8h po and DEX 1 mg q8h po	7	241.9 $\pm$ 14.1 / 168.6* $\pm$ 14.2	9.1 $\pm$ 0.6 / 2.1* $\pm$ 0.2	3/6	6/6
Roti [6]	1985	16	IOP 1 g q24h po (n = 9) SSKI 1x12 drops (456 mg iodine) q24h po (n = 7)	10	194.3 $\pm$ 9.0 / 145.4* $\pm$ 12.8 189.2 $\pm$ 16.7 / 101.6* $\pm$ 10.3	5.2 $\pm$ 0.6 / 1.2* $\pm$ 0.1 6.2 $\pm$ 0.7 / 2.2* $\pm$ 0.3	5/9 7/7	9/9 6/7
Roti [7]	1988	22	MMI 10 mg q6h po (n = 7) IOP 1g q24h po and MMI 10 mg q6h po (n = 7) SSKI 6 drops q12h po and MMI 10 mg q6h po (n = 8)	10	235 $\pm$ 36 / N.I. 199 $\pm$ 23 / N.I. 212 $\pm$ 23 / N.I.	8.7 $\pm$ 1.3 / N.I. 5.6 $\pm$ 0.8 / N.I. 5.8 $\pm$ 0.8 / N.I.	7/7 7/7 7/7	3/7 7/7 6/8
<i>Preoperative blocking regimens in patients with Graves' disease</i>								
Feek [10]	1980	10	KI 60 mg q8h po and PROP 80 mg q8h	10	225 $\pm$ 26 / N.I.	6.4 $\pm$ 0.9 / N.I.	9/10	9/10
Berghout [9]	1989	7	IOP 500 mg q24h po	5	N.I.	4.9 $\pm$ 1.8 / 1.7 $\pm$ 0.3	N.I.	5/5
Baeza [8]	1991	13	IOP 500 mg q6h po and BETA 0.5 mg q6h po and PROP 40 mg q8h po	5	284.6 $\pm$ 47.8 / 224.1* $\pm$ 53.2	6.38 $\pm$ 2.08 / 2.03* $\pm$ 0.62	0/13	13/13
Tomaski [12]	1997	14	IOP 500 mg q12h po and PTU (10/14) and BETABL	3	fT4 (pmol/l): 49.8 / 36.0*	6.9 / 2.9*	0/14	0/14
Panzer [11]	2004	17	IOP 500 mg q12h and DEX 1 mg q12h and MMI/PTU (30–40 mg/d or 450–600 mg/d in 14/17) and BETABL	7	274.8 $\pm$ 15.4 / 227.8* $\pm$ 16.7	7.7 $\pm$ 0.7 / 2.2* $\pm$ 0.2	N.I.	15/17

\* p < 0.05  
BETA = betamethasone; BETABL = beta -blocker (generic not specified); DEX = dexamethasone; IOP = iopanoic acid; KI = potassium iodide; MMI = methimazole; N.I. = not indicated in paper; nTT3 = normal total T3 after treatment; nTT4 = normal total T4 after treatment; PROP = propranolol; PTU = propylthiouracil; SSKI = saturated solution of potassium iodide

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Figures (large format)

