The Selective β_1-Blocking Agent Metoprolol Compared with Antithyroid Drug and Thyroxine as Preoperative Treatment of Patients with Hyperthyroidism

Results from a Prospective, Randomized Study

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Despite the increasing use of β-blocking agents alone as preoperative treatment of patients with hyperthyroidism, there are no controlled clinical studies in which this regimen has been compared with a more conventional preoperative treatment. Thirty patients with newly diagnosed and untreated hyperthyroidism were randomized to preoperative treatment with methimazole in combination with thyroxine (Group I) or the β_1-blocking agent metoprolol (Group II). Metoprolol was used since it has been demonstrated that the beneficial effect of β-blockade in hyperthyroidism is mainly due to β_1-blockade. The preoperative, intraoperative, and postoperative courses in the two groups were compared, and patients were followed up for 1 year after thyroidectomy. At the time of diagnosis, serum concentration of triiodothyronine (T_3) was 6.1 ± 0.59 nmol/L in Group I and 5.7 ± 0.66 nmol/L in Group II (reference interval 1.5–3.0 nmol/L). Clinical improvement during preoperative treatment was similar in the two groups of patients, but serum T_3 was normalized only in Group I. The median length of preoperative treatment was 12 weeks in Group I and 5 weeks in Group II ($p < 0.01$). There were no serious adverse effects of the drugs during preoperative preparation in either treatment group. Operating time, consistency and vascularity of the thyroid gland, and intraoperative blood loss were similar in the two groups. No anesthesiologic or cardiovascular complications occurred during operation in either group. One patient in Group I (7%) and three patients in Group II (20%) had clinical signs of hyperthyroid function during the first postoperative day. These symptoms were abolished by the administration of small doses of metoprolol, and no case of thyroid storm occurred. Postoperative hypocalcemia or recurrent laryngeal nerve paralysis did not occur in either group. During the first postoperative year, hypothyroidism developed in two patients in Group I (13%) and in six patients in Group II (40%). No patient had recurrent hyperthyroidism. The results suggest that metoprolol can be used as sole preoperative treatment of patients with hyperthyroidism without serious intra- or postoperative complications. Although the data indicate that the risk of postoperative hypothyroidism is higher after preoperative treatment with metoprolol than with an antithyroid drug, a longer follow-up period than 1 year is needed to draw conclusions regarding late results.

THE USE OF β-blocking agents in the management of patients with hyperthyroidism has gained increasing popularity in recent years,[1] and several reports have suggested the safety and efficacy of the nonselective β-blocking agent propranolol as the sole preoperative treatment of thyrotoxic patients.[2–6] Since the beneficial effects of β-blockade in hyperthyroidism are mainly due to β_1-blockade,[7,8] and since selective β_1-blocking agents have less adverse effects on pulmonary function than propranolol,[9,10] the use of a β_1-blocking agent as preoperative preparation of thyrotoxic patients may be advocated.

Only few patients managed with a selective β_1-blocking agent before thyroidectomy have been reported,[6,11] and the safety and efficacy of β_1-blocking agents as compared with a more conventional preoperative treatment has not been established. We therefore performed a prospective study in which patients with hyperthyroidism were randomized to preoperative treatment with the β_1-blocking agent metoprolol or with the antithyroid drug methimazole in combination with thyroxine. Antithyroid drug in combination with thyroxine is a well-established preoperative management of patients with hyperthyroidism.[12,13]

Patients and Methods

During the 3 years from December 1981–1984, patients with newly diagnosed and untreated hyperthyroidism were randomized to preoperative treatment with methimazole (Thacapzol®), and thyroxine (Levaxin®) (Group I) or metoprolol (Seloken®) (Group II). The diagnosis of hyperthyroidism was established on the basis of typical signs

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and symptoms, clinical diagnostic index (CDI),[14] increased serum concentrations of thyroid hormones, and suppressed serum thyroid-stimulating hormone (TSH) response to 200 μg of intravenously administered thyrotropin-releasing hormone (TRH). When CDI was calculated, numerical values were assigned to individual signs and symptoms of hyperthyroidism. A CDI greater than +19 strongly suggests hyperthyroidism.[14]

Thirty consecutive patients who were to have surgery for hyperthyroidism were randomized to one of the treatment groups by a closed envelope system. The randomization was stratified with a serum triiodothyronine (T_3) level two times the upper limit of the normal reference range (1.5–3.0 nmol/L) dividing the strata. Patients with heart block or cardiac failure and patients in whom treatment had already begun when referred to us were not included in the study. For each patient, a protocol was carried into which were entered data regarding predetermined preoperative, intraoperative, and postoperative parameters.

Fifteen patients (3 men, 12 women; mean age: 36 years, range: 25–48 years) were randomized to Group I. The diagnosis was Graves' disease in 12 patients, toxic multinodular goiter in one patient, and toxic adenoma in two patients. Patients were treated with methimazole (15–40 mg/day in 3 or 4 divided oral doses) until symptoms of hyperthyroidism disappeared and serum levels of thyroid hormones were normal, but for not less than 4 weeks. Thereafter, thyroxine (0.15 mg/day) was administered in combination with methimazole for at least 4 weeks until operation. Hence, the minimum time of preoperative treatment in Group I was 8 weeks, but the actual time for operation was also influenced by the number of patients on the waiting list for elective surgery. The last doses of methimazole and thyroxine were taken in the evening before operation, and no drugs were given after operation.

Fifteen patients (2 men, 13 women; mean age: 39 years, range: 21–59 years) were randomized to Group II. The diagnosis was Graves' disease in nine patients, toxic multinodular goiter in two patients, and toxic adenoma in four patients. The initial dose of metoprolol was 200 mg/day in 4 divided oral doses. This was increased to 400 mg/day if resting pulse rate was higher than 75 beats/min and/or clinical symptoms had not improved after treatment for 1 week. If resting pulse rate was above 90 beats/min after treatment for 1 week with 400 mg/day, the patient was excluded from the study and was given conventional preoperative treatment. The last preoperative dose of metoprolol was administered orally the morning of operation. Medication was resumed in the afternoon of operation and was continued during the first postoperative week.

Patients were premedicated with promethazine and meperidine 1 hour before general anesthesia, which was induced by thiopental sodium and maintained during controlled ventilation with fentanyl-nitrous oxide. Suxamethonium and pancuronium were used for muscle relaxation. A biopsy specimen was taken from the sternohyoid muscle as the first procedure of the operation for the study of muscle protein synthesis and degradation rates *in vitro*[15] or muscle fiber type composition.

In patients with toxic adenoma, hemithyroidectomy was performed. In patients with Graves' disease or toxic multinodular goiter, a subtotal resection was done. The thyroid lobes were mobilized, the recurrent laryngeal nerves and at least three parathyroid glands were identified, and the inferior thyroid artery was ligated truncally on each side before resection. The parathyroid glands were dissected below the line of resection with maintained vascular supply. The size of the thyroid remnant was approximately 1 × 1.5 × 2.5 cm. The operative blood loss was estimated by weighing all sponges used at operation.

Indirect laryngoscopy was performed in all patients before and after operation. During the postoperative course, pulse rate, body temperature, and serum calcium levels were determined daily. Serum T_3 and TSH were measured 1, 3, 6, and 12 months after operation.

Informed consent was obtained from each patient. The study was approved by the Ethical Committee at the University of Göteborg, Göteborg, Sweden.

Results are given as mean ± SEM unless stated otherwise. Student's t-test or Fisher's exact test was used for statistical comparisons.

Results

Preoperative Course

At the time of diagnosis the severity of the disease was similar in the two groups, as illustrated by CDI and serum T_3 (Fig. 1). Six patients in Group I and four patients in Group II had serum T_3 levels above 6 nmol/L, and the mean serum T_3 concentrations in these patients were 8.4 ± 0.73 nmol/L and 8.8 ± 1.51 nmol/L, respectively. Clinical improvement occurred faster in Group II than in Group I, and patients often had notable relief of symptoms within the first or second day of treatment with metoprolol. At the end of preoperative treatment all patients were clinically euthyroid, but serum T_3 was normalized only in Group I (Fig. 1). Resting pulse rate was reduced from 105 ± 4 to 83 ± 3 beats/min during preoperative treatment in Group I and from 110 ± 4 to 77 ± 2 beats/min in Group II.

Finger tremor was present in 11 patients in each group at the time of diagnosis. This symptom was relieved during preoperative treatment in nine of the 11 patients in Group I (82%) and in five of the 11 patients in Group II (45%) (NS). One patient in each group had moderate exoph-

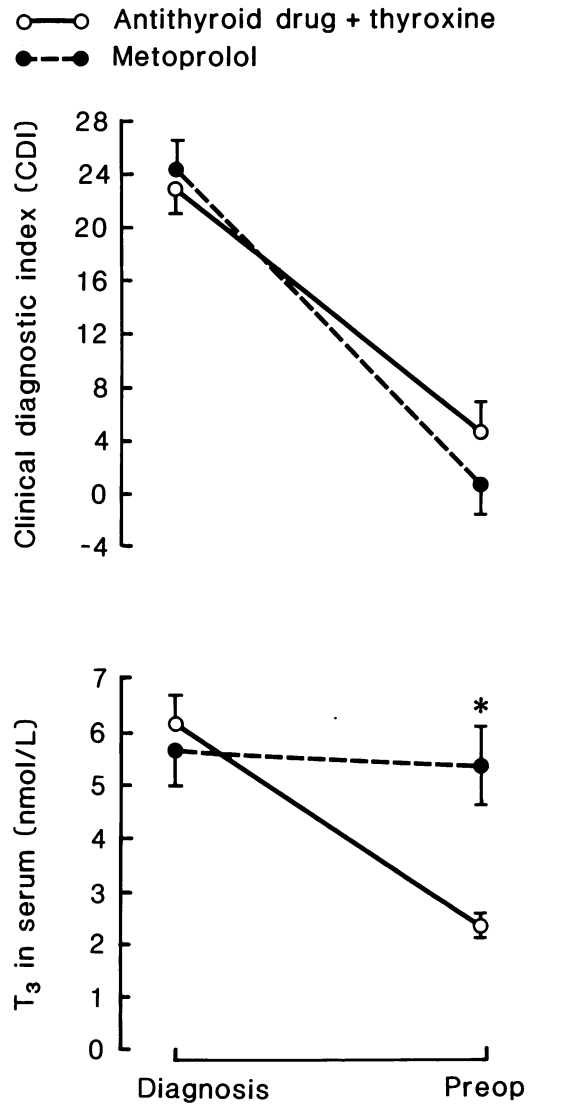

FIG. 1. Clinical diagnostic index (CDI) and serum T_3 at the time of diagnosis and before operation. Asterisk notes $p < 0.01$ *vs.* antithyroid drug + thyroxine.

thalmos at the time of diagnosis. In both patients the condition remained stationary during preoperative treatment.

The dose of metoprolol was increased from 200 mg/day to 400 mg/day in 11 of the 15 patients in Group II (73%). The median length of preoperative treatment was 12 weeks in Group I (range: 9–21 weeks) and 5 weeks in Group II (range: 4–18 weeks) ($p < 0.01$). All patients completed the preoperative treatment in the original group and had thyroid resection. Three patients (20%) in Group I had a skin rash with itching during the preoperative treatment. These symptoms disappeared when thiamazol was replaced with propylthiouracil (Tiotil®). No cases of leukopenia, agranulocytosis, or other adverse effects of the antithyroid drugs were noted. Two patients in Group II (13%) complained of nightmares during treatment with metoprolol, but symptoms were mild and vanished spontaneously after about 1 week despite continued medication. No other adverse effects were observed in Group II.

Intraoperative Course

The intraoperative course was similar in the two groups. Operative blood loss was 256 ± 35 mL in Group I and 216 ± 56 mL in Group II (NS). The operating time was 139 ± 6 minutes in Group I and 139 ± 9 minutes in Group II (NS). The consistency and vascularity of the gland was similar in the two groups of patients. There was no difference between Group I and II regarding technical difficulty in performing the thyroidectomy. The weight of the resected thyroid tissue was 27 ± 3.3 g in Group I and 29 ± 3.2 g in Group II (NS). No anesthesiologic or cardiovascular complications occurred in either group. Initial, maximum, and minimum blood pressure and pulse rate recorded during operation were similar in Groups I and II (Fig. 2).

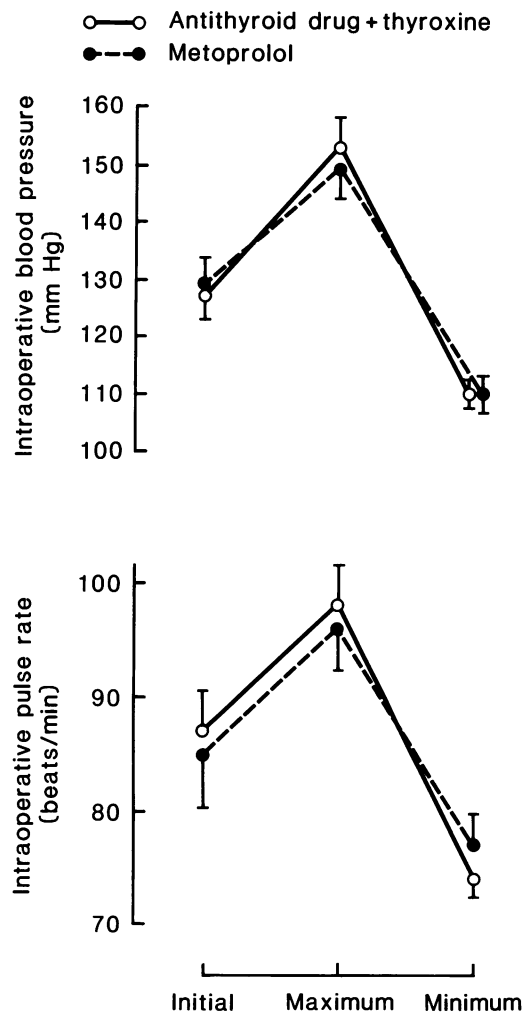

FIG. 2. Initial, maximum, and minimum intraoperative systolic blood pressure and pulse rate in patients who had thyroidectomy.

Postoperative Course

All patients in Group II recommenced the oral intake of metoprolol in the afternoon of operation. One patient in Group I and three patients in Group II experienced flushing and sweating, elevated body temperature, and tachycardia within the first postoperative hours. These symptoms and signs were relieved by the administration of 50 mg of metoprolol orally to the patient in Group I and by 2.0–20 mg of metoprolol intravenously to the patients in Group II. There were no cases of severe reactions or thyroid storm after operation in any of the treatment groups. Morning pulse rate and body temperature at operation and 3 days after thyroidectomy are shown in Figure 3. Except for a significantly lower pulse rate in Group II than in Group I in the morning of operation, no other differences in pulse rate or body temperature were noted between the two groups.

One patient in Group I had reoperation 6 hours after thyroidectomy due to bleeding from a small artery in the thyroid capsule. There were no cases of permanent recurrent laryngeal nerve paralysis, postoperative hypocalcemia, or other complications in either group. The postoperative hospital stay was 3.5 ± 0.3 days in Group I and 3.4 ± 0.2 days in Group II (NS).

Late Results

Hypothyroidism developed in two patients in Group I (13%) and in six patients in Group II (40%) during the first postoperative year (NS) and was treated with thyroxine (0.1–0.2 mg/day). In Group I, two other patients were given thyroxine after operation since histopathologic examination of resected thyroid tissue showed significant lymphocyte infiltration and a small papillary carcinoma, respectively. The latter patient was reoperated with total lobectomy on the affected side.

Both patients in Group I and four patients in Group II who had postoperative hypothyroidism suffered from Graves' disease. The diagnosis of the other patients in Group II was toxic multinodular goiter and toxic adenoma, respectively. The weight of the resected thyroid tissue was 34 ± 3.1 g in patients who had hypothyroidism and 25 ± 2.8 g in patients who were euthyroid during the first postoperative year ($p < 0.05$).

Recurrent hyperthyroidism was not seen in any of the patients during the first postoperative year.

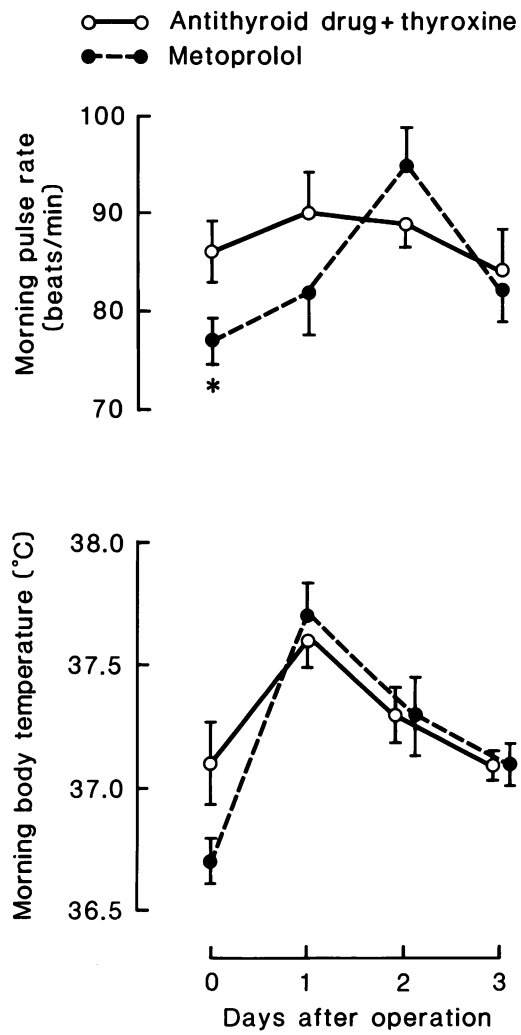

FIG. 3. Morning pulse rate and body temperature on the day of operation (before operation) and 3 days after thyroidectomy. Asterisk notes $p < 0.05$ *vs.* antithyroid drug + thyroxine.

Discussion

Postoperative treatment of patients with hyperthyroidism with antithyroid drug and thyroxine is well established, and a large number of patients have been reported with a low incidence of intraoperative and postoperative complications after this type of preparation.[12,13] At the time of surgery the patients are euthyroid, the gland is depleted of hormone due to inhibited synthesis by the antithyroid drug, and the thyroid is firm and small in size due to the TSH-inhibiting effect of thyroxine treatment.[13]

The use of β-blocking agents in the preoperative preparation of patients with hyperthyroidism has been described in several reports over the last 10–15 years.[2-6] With this regimen, fast relief of symptoms is achieved, and patients can have surgery a couple of days to a few weeks after initiation of treatment. Furthermore, the risk of some of the adverse effects of antithyroid drugs, such as leukopenia and agranulocytosis, is avoided. However, since hormone production is not blocked and serum thyroid hormones remain elevated during treatment with β-blockers, concerns have been expressed for increased risk of intraoperative complications and postoperative thyroid storm,[16-19] and some authors advocate that β-blockers

should only be used in patients with mild or moderate thyrotoxicosis.[20]

In view of the established safety of thyroidectomy in conventionally prepared patients, it is essential that the β-blocker regimen should be comparably safe. To the best of our knowledge no prospective and randomized study has been reported previously, in which preoperative treatment of patients with hyperthyroidism with a β-blocking agent was compared with a conventional preoperative regimen. However, the large number of patients successfully treated with propranolol probably justifies the conclusion that this substance is safe and efficient in the preoperative management of patients with thyrotoxicosis.[5,6] The current study suggests that the selective β_1-blocking agent metoprolol can also be used as preoperative treatment in patients with hyperthyroidism, without increased risk of serious intra- or postoperative complications compared with a conventional regimen. A selective β_1-blocking agent may be preferable to a nonselective β-blocker, since the effect of this type of treatment in hyperthyroidism is caused mainly by β_1-blockade.[7,8] Also, β_1-blocking agents have less adverse effects on pulmonary function than nonselective β-blockers.[9,10] This was illustrated in a recent report, in which two thyrotoxic patients with asthma were successfully treated with metoprolol before thyroidectomy.[11] In one of those patients, propranolol was initially administered but had to be discontinued after wheezing and tachypnea developed.

Preoperative Course

Advantages of β-blockers claimed over conventional pretreatment include fast relief of hyperthyroid symptoms and short preparation time. Many of our patients treated with metoprolol had notable improvement of symptoms within the first or second day of treatment, despite the fact that the initial dose of metoprolol was too small to reduce pulse rate to 75 beats/min within the first week in two thirds of the patients.

Although most of the adrenergic symptoms in hyperthyroidism can be controlled by β_1-blockade,[7,8] previous reports suggest that finger tremor is mediated mainly by β_2-receptors.[8,21] The current study supports that hypothesis. Finger tremor was only abolished in less than half of the patients in Group II, whereas this symptom disappeared during preoperative treatment in the majority of patients in Group I.

The risk of agranulocytosis during treatment with antithyroid drugs is small, but when it occurs it is life threatening. No patient in our study had agranulocytosis. In a previous report the incidence of this complication was 2.7% among patients with thyrotoxicosis treated with methimazole.[13] Agranulocytosis has not been reported in patients with hyperthyroidism treated with β-blocking agents.

The incidence of allergic skin reactions in our patients treated with methimazole (20%) was somewhat higher than reported previously.[13] However, no reaction was severe, and symptoms disappeared when methimazole was substituted with propylthiouracil. Sleep disturbances during treatment with β-blockers have been described before and was more common during treatment with propranolol than metoprolol.[8]

Intraoperative Course

Friability and vascularity of the thyroid gland are important factors when different preoperative treatments are evaluated. Although it is generally agreed on that the gland is firm and less vascular after treatment with antithyroid drug and thyroxine,[12,13] reports on the appearance of the gland after preoperative treatment with β-blocker have been conflicting. Some authors reported that the gland was less friable and vascular after propranolol than after conventional pretreatment.[3,5,22] Others found the gland to be more vascular and friable than after pretreatment with antithyroid drug and thyroxine, and some even reported difficulties in obtaining adequate hemostasis after preoperative treatment with propranolol.[16,18,19] The current result of similar operative blood loss suggests that the vascularity of the gland was not different between the two groups. This is in accordance with the impression during operation that there were no differences in consistency or vascularity of the gland between the two groups. No technical difficulties were encountered during operation in either group. One case of postoperative bleeding in Group I was caused by hemorrhage from a small artery in the thyroid capsule and could not be related to friability or vascularity of the gland.

The amount of operative blood loss reported here was almost identical to a recent study by Lee et al.,[23] but was larger than in other series of thyroidectomies. Thus, Feely et al.[20] reported a blood loss of 80–100 mL and Lee et al.[5] reported a blood loss of 98 ± 10 mL. In none of those studies, however, the method for estimation of blood loss was stated. In one series of patients with hyperthyroidism, prepared with propranolol, in which blood loss was measured by weighing the gauze swabs used at operation, the blood loss was 160 ± 20 mL.[3] Michie, with a series of 1500 patients with thyrotoxicosis,[22] stated that thyroidectomy could be performed with blood loss as small as 15–20 mL.

No cardiovascular complications occurred during anesthesia in the current study. Similarly, anesthesia was reported to be uneventful in most previous series of patients with hyperthyroidism who were prepared with a β-blocker. However, in one study of 44 patients with thyrotoxicosis who were prepared with propranolol, unifocal ventricular ectopies were noted during operation in three

patients and transient atrial fibrillation was noted in one patient.[20]

Postoperative Course

Despite the fact that all patients took their last dose of metoprolol in the morning of operation, three patients (20%) in Group II had clinical signs of hyperthyroid function in the immediate postoperative course. The symptoms were abolished by small doses of metoprolol administered intravenously, and no case of thyroid storm was seen. Postoperative clinical signs and symptoms consistent with high hormone levels were reported previously in 10–20% of patients pretreated with propranolol.[4,6,20] In these patients, symptoms were relived by intravenous or oral administration of small doses of propranolol. In one series, similar postoperative symptoms were seen in two of eight patients prepared with propranolol, and in that study high doses of cortisone were given intravenously in combination with the β-blocker, since development of hyperthyroid crisis was feared.[16] In a more recent study, one of 22 patients pretreated with propranolol died of thyrotoxic crisis 3 days after thyroidectomy.[23] The amount of propranolol administered in that study, however, was probably inadequate (120 mg/day), as illustrated by high baseline and intraoperative pulse rates. Although it is likely that the immediate postoperative symptoms were caused by high thyroid hormone levels, the fact that one of our patients in Group I had similar symptoms indicates that this clinical picture can also be a nonspecific reaction to this type of operation.

The incidence of postoperative hyperthyroid symptoms in patients prepared with β-blockers illustrates the need for careful supervision of patients, especially during the first 24 postoperative hours. It is essential that the medication is continued until immediately before operation, and the interval between β-blocker dose and operation should not exceed 3–4 hours. It is likewise important that medication is reinstituted immediately after operation. If nausea or vomiting should prevent oral intake, the drug should be given intravenously. Normalization of serum T_3 and T_4 was demonstrated 3–4 days after thyroidectomy in patients prepared with propranolol,[3,4] and it is probably not necessary to continue β-blocker treatment for 1 week after operation, as we did in this study.

Late Results

The frequency of postoperative hypothyroidism was relatively high in the current study, especially in Group II. In other reports, the frequency of hypothyroidism varied from less than 10%[13,24,25] to 50%.[26,27] Since the postoperative thyroid function is related to the size of the thyroid remnant,[28] our results of a relatively high frequency of hypofunction, together with the absence of recurrent hyperthyroidism during the first postoperative year, indicate that a larger thyroid remnant could have been left in place in many of the patients. The larger amount of resected thyroid tissue in patients with postoperative hypothyroidism than in patients who became euthyroid supports that suggestion. It should be noted, however, that there was no difference in the size of the resected specimen between Groups I and II; any difference in the frequency of postoperative hypothyroidism between the two groups could not be ascribed to differences in the extent of dissection.

The incidence of hypothyroidism continues to increase at least for 5–6 years after thyroidectomy.[28] Thus, a longer follow-up time is required to evaluate if postoperative hypofunction is more common after preoperative treatment with metoprolol than with antithyroid drug and thyroxine, as our results 1 year after thyroidectomy indicate.

In conclusion, this prospective, randomized study suggests that the selective β_1-blocking agent metoprolol can be used as a preoperative preparation of patients with hyperthyroidism, offering the advantage of a shorter preoperative treatment than with a conventional regimen. Whether metoprolol is superior to the more frequently used propranolol cannot be answered from this study, but since the adrenergic symptoms in hyperthyroidism are mainly mediated by β_1-receptors, the use of a selective β_1-blocking agent may be advocated.

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