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The preoperative thyroid function and perioperative course in patients with Graves' disease

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Graves' disease is an autoimmune disorder that induces increase in thyroid hormone production and release. Although euthyroid should be desirable to ensure a safe operation, some patients still undergo thyroidectomy with hyperthyroidism. The aim of this study was to evaluate our preoperative strategies in patients with Graves' disease. A total of 186 patients underwent thyroidectomy for Graves' disease between 2003 and 2017. We gave all of these patients potassium iodide (KI) in order to decrease their thyroid hormone levels. We compared the clinical factors among three groups defined by the value of serum free triiodothyronine (FT3) after the administration of KI: (1) the good control group (n=126) with ≤6.0 pg/mL, (2) the fair control group (n=35) with >6.0 but ≤10.0 pg/mL, and (3) the poor control group (n=25) with >10.0 pg/mL. KI decreased the serum levels of thyroid hormone. However, some patients still had hyperthyroidism, and the subsequent administration of corticosteroid reduced FT3 but not thyroxine. Regarding the intraoperative course, the heart rate at 1 h after beginning general anesthesia was higher in the poor control group than in the good control group ($p<0.05$), and the proportion of patients given adrenergic beta-blocker was higher in the poor control group than in the other groups ($p<0.01$ each). One patient in the fair control group experienced suspected thyroid storm after total thyroidectomy. The occurrence rate of other deteriorations was identical among the three groups. With preparative KI and corticosteroid administration, almost all patients with Graves' disease were able to undergo thyroidectomy safely.

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Introduction

Graves' disease (GD) is an autoimmune disorder in which thyrotropin receptor antibodies (TRAbs) stimulate the thyroid-stimulating hormone (TSH) receptor, which induces increased thyroid hormone production and release. GD is the most common cause of hyperthyroidism in adults.[1] Triiodothyronine (T3), the active form of thyroid hormone, is responsible for the cellular actions caused by thyroid hormone. It binds to specific nuclear receptors and influences most of the tissues and organs. Additionally, thyroid hormone has the nongenomic actions, which begin at receptors in the plasma membrane, mitochondria or cytoplasm.[2] The nongenomic actions affect angiogenesis, cell proliferation, cellular respiration in mitochondria, and so on.[2] Thyrotoxicosis, defined as the effects due to an excess of thyroid hormones in the bloodstream, induces specific symptoms, including increases in thermogenesis and the basal metabolic rate, weight loss,

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osteoporosis, tremor, and neuropsychiatric symptoms, such as anxiety.[3] Disorders in the cardiovascular system may be the most profound, including atrial fibrillation, pulmonary hypertension, and rarely cardiovascular collapse and death.[3, 4]

Three options are available to manage GD: anti-thyroid drug (ATD), radioactive-iodine (RAI) treatment, and surgery. The prevalence of therapy varies among different countries. For instance, ATD is the first-line therapy in most Japanese patients, while RAI is more preferred in the United States[5]. Furthermore, while thyroidectomy has been regarded as a prompt and certain therapy for GD, it has some drawbacks, including operative scarring, the need for hospitalization, and complications, such as recurrent laryngeal nerve (RLN) paralysis, hypoparathyroidism, and intraoperative bleeding.[1, 6] Nevertheless, patients who are suspected of having malignancy, unwilling to undergo RAI treatment, pregnant or lactating, and unable to tolerate ATD or contraindicated for RAI, such as those with Graves' ophthalmopathy, are still good candidates for surgery.

The 2016 American Thyroid Association (ATA) Guidelines recommend that a potassium iodide (KI)-containing preparation should be given in the preoperative period to reduce the risk of thyroid storm by stabilizing the thyroid function.[7] KI is additionally beneficial because it decreases the thyroid blood flow and vascularity, which can otherwise lead to intraoperative blood loss during thyroidectomy. [7]

However, while we have given KI to patients preoperatively according to the ATA Guideline, some still have hyperthyroidism at surgery. In these patients, we administer corticosteroids and/or beta-blockers in the perioperative period, which are also recommended in the ATA Guideline. In the present study, we analyzed the efficacy of our perioperative strategies for patients undergoing thyroidectomy for GD and evaluated their feasibility.

Materials and Methods

We analyzed the clinical and laboratory data of 186 consecutive patients with GD who had undergone thyroidectomy between January 2003 and December 2017 in our department. The study was approved by the Institutional Review Board of our institution, and the requirement to obtain informed consent was waived.

GD was defined by the presence of thyrotoxicosis, a diffuse goiter, and serum TRAb. In terms of preparation for surgery, all patients were administered 50 mg of KI twice a day, for a median period of 14 days. Both before and after the administration of KI, we evaluated the thyroid function. If the improvement of thyrotoxicosis was insufficient, adrenal corticosteroid was given orally or intravenously in order to suppress the conversion of thyroxine (T4) to T3, which is the active form of thyroid hormone. Reference ranges of thyroid hormones are 2.3-4.3 pg/mL for free T3 (FT3), 0.9-1.7 ng/dL for free T4 (FT4) and that of TRAb is <1.0 IU/L.

Surgery was performed under general anesthesia in all patients. To compare clinical factors according to the thyroid function, we divided the patients into three groups based on the value of FT3 after administration of KI (Figure 1): (1) the good control group included patients whose value of FT3 was ≤6.0 pg/mL, (2) the fair control group included patients whose value of FT3 was >6.0 but ≤10.0 pg/mL, (3) the poor

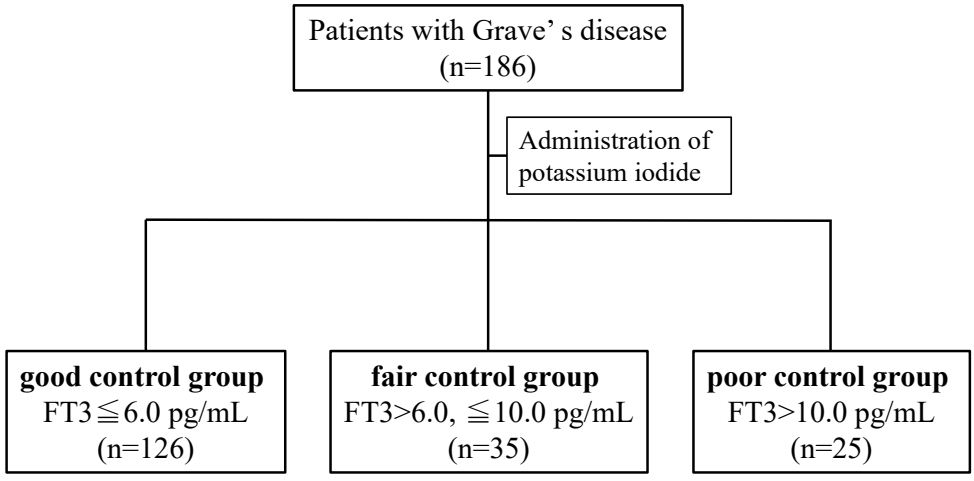

Figure 1. Study cohort inclusion flowchart. The patients were divided into three groups based on the value of free triiodothyronine (FT3) after the administration of potassium iodide.

control group included patients whose value of FT3 was >10.0 pg/mL. The operations were performed with conventional open surgery or video-assisted neck surgery (VANS). According to the extent of thyroidectomy, we used the following operative methods: (1) subtotal thyroidectomy, with at least two grams of remaining thyroid tissue, (2) near-total thyroidectomy, with less than two grams of remaining tissue, and (3) total thyroidectomy. The operative methods were selected by the surgeons. We placed closed suction drainage tubes before wound closure in all patients but one. Recurrent laryngeal nerve (RLN) injury was recorded if a voice change occurred. Calcium supplements and vitamin D analog were given to patients with symptomatic hypocalcemia. Those patients who were able to discontinue the supplements with normocalcemia within 12 months after surgery were categorized as having transient hypocalcemia, whereas those who had to continue for more than 12 months together with a below-normal serum intact parathyroid hormone level were diagnosed with permanent hypoparathyroidism.

The data are presented as the median (range). A paired *t* test was performed for comparisons between pretreatment and posttreatment values of FT3 and FT4. A one-way analysis of variance (ANOVA) was performed to compare continuous variables among the three groups, and for $p<0.05$, the Tukey-Kramer test was applied for multiple comparisons. The chi-square test was used to compare categorical variables. For all tests, $p<0.05$ was considered to be statistically significant. The statistical analyses were performed with the StatMate III software program for Macintosh (ATMS Co., Ltd., Tokyo, Japan).

Results

Clinical variables according to the value of FT3 after administration of KI

All of the patients took KI before surgery for a mean 14 days (6-330), and the mean values of FT3 and FT4 were significantly lower after taking KI than those before (8.3 pg/mL [2.0-32.6] versus 4.6 pg/mL [1.3-33] for FT3, $p<0.01$; 2.7 ng/dL [0.2-11.0] versus 1.4 ng/dL [0.1-6.0] for FT4, $p<0.01$) (Figure 2). The mean preoperative hospital stay was 3 days (0-7).

Table 1 shows the background characteristics of patients in three groups according to the thyroid function after KI administration. The age, sex, period of KI administration, and period between the disease onset and surgery were roughly the same among the three groups. However, the values of FT3 and FT4 at the initial consultation (before KI administration) differed among the groups. In detail, the FT3 in both the fair and poor control groups was significantly higher than in the good control group ($p<0.01$, each), as was the FT4. The TRAb in both the fair and poor control groups was significantly higher than in the good control group ($p<0.01$ each). The proportion of patients who continued with ATD until thyroidectomy in the good control group was significantly higher than in the fair control group ($p<0.01$).

Table 2 shows the variables of the perioperative clinical factors. The proportion of patients who took adrenergic beta-blocker preoperatively in the poor control group was significantly higher than in either the good or fair control group ($p<0.01$, $p<0.05$ each). More patients in both the fair and

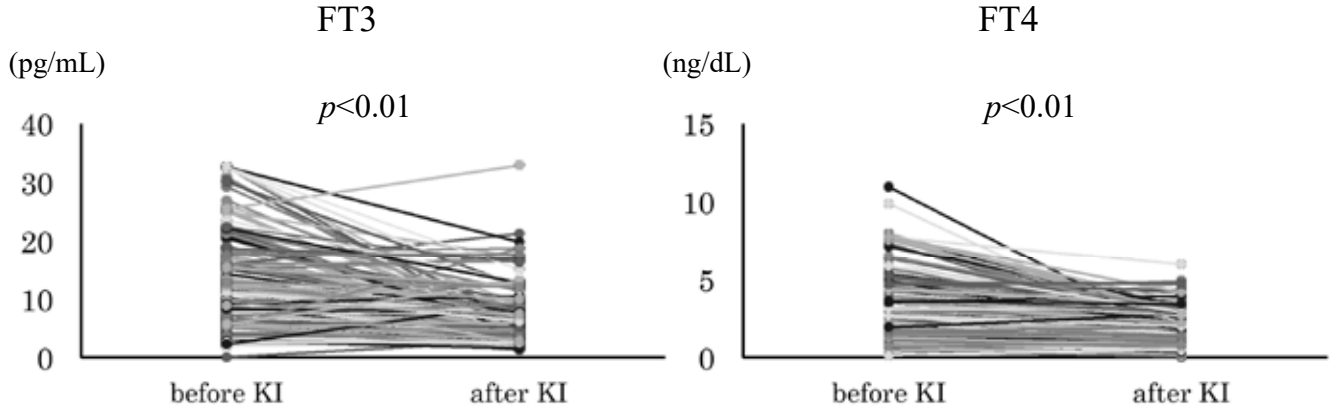

Figure 2. Changes in serum levels of free triiodothyronine (FT3) and free thyroxine (FT4) by the administration of potassium iodide (KI).

poor control groups took corticosteroid preoperatively than in the good control group ($p<0.01$, each). With regard to the variables during the operation, the heart rate at 1 h after beginning general anesthesia in the poor control group was significantly higher than in the good control group ($p<0.05$), and the proportion of patients who were given beta-blockers during the operation was higher in the poor control group than in the good or fair control group ($p<0.01$ each). The duration of surgery, amount of blood loss, and thyroid weight were not markedly different among the three groups. With regard to the complications by operation, thyroid storm was seen one patient only in the fair control group.

A 13-year-old girl with 21-trisomy and intellectual disability underwent elective total thyroidectomy. Her FT3 level immediately before surgery was 9.9 pg/mL. Although total thyroidectomy was completed without any trouble, she experienced convulsion, a decreased level of consciousness, and sursumvergence at 1 day after surgery. We suspected that these symptoms were due to thyroid storm. The symptoms subsided spontaneously without any sequelae. The rates of other complications did not differ markedly among the three groups. The duration of the postoperative hospital stay was roughly the same among the groups.

A comparison of clinical variables between the patients with or without corticosteroids

In the patients who took corticosteroids in the poor control group, the value of FT3 was significantly lower after taking corticosteroids than before (14.1 pg/mL [10.1-33.0] versus 9.9 pg/mL [3.5-19.2], $p<0.05$), but that of FT4 was not (3.0 ng/dL [0.9-4.8] versus 3.7 ng/dL [1.1-9.8], $p=0.24$) (Figure 3). Among the patients in the poor control group, we compared clinical factors between those with and without corticosteroid administration but noted no marked differences (Table 3). The methods (orally or intravenously), the doses, and durations of adrenal corticosteroid administration varied among patients, decided by the physicians (data not shown). No patients took steroid pulse therapy.

Table 1. Background characteristics of patients

	Good control (n=126)	Fair control (n=35)	Poor control (n=25)	P
Age (years)	35 (13-75)	33 (13-62)	31 (11-61)	0.42
Period of KI administration (days)	14 (6-157)	14 (6-330)	15 (7-136)	0.29
Sex, male:female	32:93	6:29	6:19	0.60
Period between disease onset and surgery (months)	24 (2-300)	12 (1-240)	15 (1-180)	0.29
Preoperative free T3 at initial consultation (pg/mL)	6.1 (2.0-32.6)	13.5 (2.3-30.4)	17.7 (5.3-32.6)	<0.01
Preoperative free T4 at initial consultation (ng/dL)	2.0 (0.3-9.8)	4.5 (0.2-11.0)	4.4 (0.8-8.0	<0.01
Serum TRAb (IU/mL)	9.9 (0.9-431.2)	30.4 (3.3-1158.7)	66.6 (2.7-318.6)	<0.01
Patients taking anti-thyroid drugs until thyroidectomy	53.2%	28.6%	44.0%	<0.05

TRAb, thyrotropin receptor antibody.

Table 2. Variables of perioperative clinical factors

	Good control (n=126)	Fair control (n=35)	Poor control (n=25)	P
Patients taking beta-blockers preoperatively	38.1%	45.7%	72.0%	<0.01
Patients taking corticosteroids preoperatively	5.6%	42.9%	68.0%	<0.01
Duration of surgery (min)	173 (69-361)	183 (110-305)	182 (120-380)	0.83
Amount of blood loss (mL)	85 (10-1250)	120 (20-560)	100 (10-1390)	0.21
Heart rate at 1 h after beginning general anesthesia (/min)	63 (45-107)	63 (55-85)	73 (56-95)	<0.05
Administration of beta-blockers during surgery	8.3%	0.0%	50.0%	<0.01
Weight of thyroid (g)	44 (9-369)	41 (21-416)	54 (20-624)	0.27
Presence of tetany	34.5%	39.4%	50.0%	0.35
Permanent RLN palsy	0.8%	0.0%	0.0%	0.79
Permanent hypoparathyroidism	0.8%	0.0%	4.8%	0.24
Thyroid storm	0.0%	2.9%	0.0%	0.11
Postoperative hospital stay (days)	4 (2-22)	5 (3-11)	4 (3-9)	0.69

RLN, recurrent laryngeal nerve.

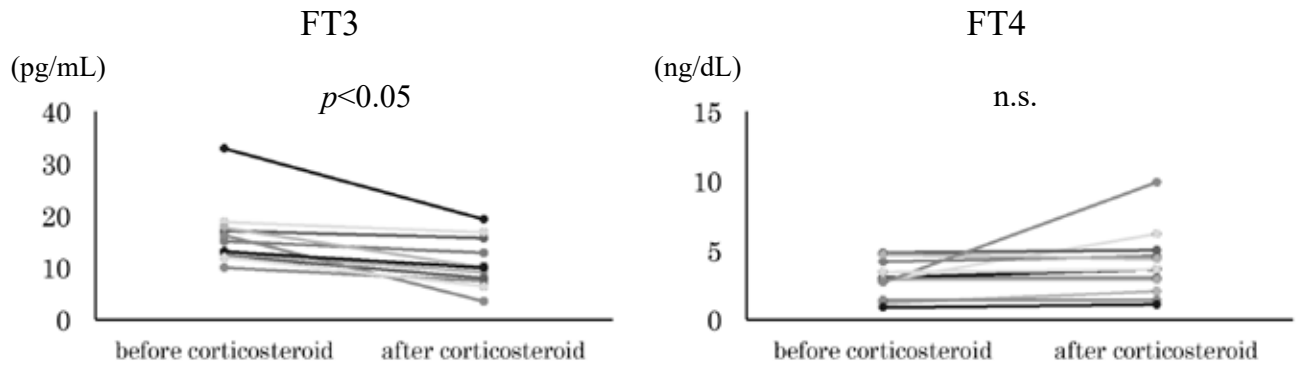

Figure 3. Changes in serum levels of free triiodothyronine (FT3) and free thyroxine (FT4) by the administration of corticosteroids in patient with thyrotoxicosis even after administration of potassium iodide and/or anti-thyroid drug. n.s.; not significant.

Table 3. Variables of clinical factors in the patients in the poor control group with or without corticosteroid administration

	With corticosteroids (n=17)	Without corticosteroids (n=8)	P
Age (years)	36 (11-61)	29 (17-40)	0.43
Sex, male:female	5:12	1:7	0.35
Free T3 after administration of KI (pg/mL)	15.0 (10.1-133.0)	13.0 (10.5-19.8)	0.82
Free T4 after administration of KI (ng/dL)	3.0 (0.9-4.8)	3.2 (1.0-6.0)	0.68
Patients taking beta-blockers preoperatively	76.5%	62.5%	0.47
Duration of surgery (min)	174 (120-380)	222 (130-255)	0.21
Amount of blood loss (mL)	90 (10-1390)	155 (30-560)	0.26
Presence of tetany	35.3%	25.0%	0.49
Permanent RLN palsy	5.9%	0.0%	0.48
Permanent hypoparathyroidism	0.0%	2.0%	0.15
Thyroid storm	5.9%	0.0%	0.47
Postoperative hospital stay (days)	4 (3-9)	5 (3-6)	0.82

KI, potassium iodide; RLN, recurrent laryngeal nerve

Discussion

We compared the clinical factors in the patients according to the thyroid function after the administration of KI for 14 days (median) as preoperative preparation. The predictive factors for increased thyroid function even after KI administration were, increased initial thyroid function, high value of TRAb, and non-continuation of ATD. Emerson et al.[8] showed that iodide alone was not adequate for the control of hyperthyroidism. In the short term, excessive KI inhibits the enzyme thyroid peroxidase,[9] subsequently inhibiting the organization of iodine and attenuation of synthesis of thyroid hormones (Wolff-Chaikoff effect),[10, 11] which additionally blocks the release of thyroid hormones. Generally, there is an adaptation to excess iodine by an autoregulation within the thyroid, leading to escape from inhibition of synthesis of thyroid hormones.[12] Thus, the thyroid hormones in patients with GD treated with iodine can increase again after a period of thyroid blocking. Had we administered these patients KI for longer period, they would have attained a good thyroid function. However, we hesitated to do so because how often and how early escape becomes evident is not obvious. The patients whose thyroid function was high even after the administration of KI were given corticosteroids more frequently. During operation, these patients showed a higher heart rate and were given adrenergic beta-blockers more frequently.

Thyroid storm is a life-threatening emergency condition that can cause multi-organ failure, resulting from a hyperthyroid state. Its occurrence is associated with invasive procedure or condition, including surgery, infection, trauma, or the discontinuation of ATD in patients with hyperthyroidism, if not treated properly.[13] Its manifestations include a fever, tachycardia, supraventricular arrhythmia, central nervous system symptoms, and gastrointestinal symptoms.[14] Although its incidence is very low, occurring in 0.22% of all thyrotoxic patients, the mortality rate is relatively high (10.7%).[15] Only

one patient in the fair control group showed suspected (non-life-threatening) thyroid storm after the operation, as no other causes for her central nervous system symptoms could be detected, even though the criteria for thyroid storm were not met. In the patients whose thyroid function was high, the administration of corticosteroids immediately before operation with the intention of reducing the conversion of T4 to T3,[16] which is the active form of thyroid hormone, decreased the level of FT3 but not that of FT4.

Although GD patients are given KI to prepare them for thyroidectomy in many institutions, including our own, the efficacy of this approach seems controversial. Randle et al.[17] reported in their prospective study that KI was associated with a reduction in gland vascularity and a reduced occurrence of transient hypoparathyroidism and hoarseness, suggesting that KI improves the safety of thyroidectomy for GD. However, the routine use of KI and achieving a euthyroid state before thyroidectomy was reported to be unnecessary in a retrospective cohort study.[18] Furthermore, some reports showed that patients with hyperthyroidism undergoing thyroidectomy did not develop thyroid storm. [18, 19] A previous study reported no marked change in vital signs—but an increased requirement of anesthetic agents—in patients with uncontrolled GD who had T4 levels up to the twice the upper normal limit.[20] In another retrospective cohort study with 151 subjects, mild to moderate hyperthyroidism did not affect the intraoperative vital signs during thyroidectomy, although the use of intraoperative beta-blockers was increased.[21] Largely consistent with these previous reports, in our present study, the proportion of patients who were given beta-blockers during the operation was significantly higher in the patients with a poor thyroid function (FT3 >10.0 pg/mL) than in the good control group. However, the heart rate at 1 h after beginning anesthesia was higher in the poor control group than in the good control group, probably due to differences in the cut-off value between the previous study and our own. In the present study, patients were given landiolol hydrochloride, a short-acting intravenous adrenergic beta-blocker with high cardioselectivity and a short elimination half-life (4 min),[22] leading to it facilitating patient management, especially during the perioperative period.[23] Safe thyroidectomy was therefore able to be performed in patients with hyperthyroidism due to improvements in the anesthetic reagents available and techniques thanks to the presence of an experienced surgeon and anesthetist.

In conclusion, preoperative KI reduced serum levels of thyroid hormone in patients with GD. Some patients, however, were still hyperthyroidism. One of these patients experienced suspected thyroid storm after total thyroidectomy while occurrences of the other complications were identical regardless of preoperative thyroid function. Although we gave the KI and corticosteroid as preparation for thyroidectomy in the patients with Graves' disease, these strategies have been controversial. Prior to thyroidectomy for Graves' disease, the patients should be clinically euthyroid and FT4 and FT3 were recommended less than 30 and 10 pmol/L with medications including KI and corticosteroid.[24] In patients with insufficient decrease in thyroid hormones, additional preparative medications such as cholestyramine, lithium, carbamazepine, and plasmapheresis have been reported, to subside hyperthyroidism prior to thyroidectomy.[7, 24] Most of the cases with poor control in thyroid hormone, however, could be undergo thyroidectomy, thanks to the development of various agents and techniques, as reported previously.[22, 23] Further investigations with large number of patients are needed to reach conclusive findings on the issues.

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