Original Article

# Predictive factors for intraoperative excessive bleeding in Graves' disease.

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Abstract

Background; In Graves' disease, since a thyroid tends to have extreme vascularity, the amount of intraoperative blood loss (AIOBL) becomes large in some cases. We sought to elucidate the predictive factors of the AIOBL. Methods; A total of 197 patients underwent thyroidectomy for Graves' disease between 2002 and 2012. We evaluated clinical factors that would be potentially related with AIOBL retrospectively. Results; The median period between disease onset and surgery was 16 (range 1-480) months. Conventional surgery was performed in 125, while video-assisted surgery in 72. Subtotal and neartotal/total thyroidectomy were 137 and 60, respectively. The median weight of the thyroid was 45 (7.3-480.0) grams. The univariate analysis revealed that the strongest correlation of AIOBL was noted with weight of the thyroid ($p<0.001$). Additionally, AIOBL was positively correlated with the period between onset and surgery ($p<0.001$) and negatively with preoperative free T4 ($p<0.01$). Multivariate analysis showed that only weight

of the thyroid was correlated with AIOBL independently ($p<0.001$). Four patients (2.0%) needed blood transfusion, including 2 of autotransfusion, whose thyroids were all above 200 grams. The amount of drainage during initial 6 hours and days until drain removal was positively correlated with AIOBL ($p<0.001$, each). The occurrences of postoperative complications, such as recurrent laryngeal nerve palsy or hypoparathydoidism, were not correlated with AIOBL and neither was postoperative hospital stay. Conclusions; Huge goiter presented as predictive factors for excessive bleeding on surgery for Graves' disease and preparation for blood transfusion should be considered in the cases of thyroid above 200 grams.

Key words; Graves' disease, intraoperative blood loss, thyroidectomy

Introduction

Graves' disease (GD) is an autoimmune disease, in which thyroid-receptor antibodies combine to the thyrotropin receptor, resulting in promoting production of thyroid hormones in the follicular cells through stimulation of cyclic adenosine monophosphate.[1] GD is the most common cause of hyperthyroidism. Acceptable therapeutic options are antithyroid drug (ATD), radioiodine therapy (RI), and surgery.[1, 2] Prevalence of therapy varies in different parts of world. ATD is the first-line therapy in the most of the Japanese patients while RI is more preferred in the United State.[1] Although in Japan, total number of the patients who took RI were much fewer than that in Europe or the United State,[3] RI has spread due to the new regulation that allows RI undergone at outpatient clinic.[4] Nevertheless, the cases with suspicious of malignancy, with unwillingness to take RI, and in pregnancy should still be good indications for surgery. While thyroidectomy has been regarded as prompt and assured therapy for GD, it has some drawbacks, namely, operative scar, to need hospitalization, complications related to operation

including recurrent laryngeal nerve (RLN) paralysis, hypoparathyroidism, and intraoperative bleeding.[1, 2] Especially, thyroid gland of GD tends to have hypervascularity and hemostasis is often troubling.[5, 6] In this study, we evaluated the factors that were relevant to the amount of intraoperative blood loss (AIOBL), and how AIOBL affected postoperative courses retrospectively.

## Methods

We reviewed the clinical and laboratory data of 197 consecutive patients with GD, in whom thyroidectomy was performed between April 2002 and March 2012 at our department. The patients that had undergone neck surgery before were excluded. GD was defined by the presence of thyrotoxicosis, a diffuse goiter, and serum TSH receptor antibody or thyroid stimulating antibody. After the operation, the diagnosis was confirmed histologically in all patients. In terms of preparation for surgery, all patients were given potassium iodide for the median period of 14 days. The operations were performed with

conventional open surgery or video-assisted neck surgery (VANS). The indications and technique of VANS was described previously.[7] Subtotal thyroidectomy was defined with remaining thyroid tissue between 2 and 6 gram and neartotal thyroidectomy with less than 2 gram.

We put closed suction drainage tubes before wound closure in all the patients except one and removed them 1 to 3 days later. Recurrent laryngeal nerve (RLN) injury was recorded if voice change was recognized. Calcium supplements and vitamin D analogue were given to those with symptomatic hypocalcemia. Those patients who could discontinue the supplements with normocalcemia within 12 months after surgery were defined as transient hypocalcemia, whereas those who had to continue for more than 12 months together with a below-normal serum intact parathyroid hormone level were categorized as permanent hypoparathyroidism.

Clinical variables were assessed in relation to AIOBL. Univariate analysis was performed by single regression analysis to test correlation between

continuous variables and AIOBL, and Student t test was used to compare between groups. A p value of less than 0.05 was considered statistical significant. For multivariate analysis, the factors identified as being associated with a p value $\leqq 0.10$ were entered into a stepwise regression analysis to determine the independent risk factors for AIOBL. Statistical analysis was performed with StatMate III for Macintosh (ATMS Co., Ltd, Tokyo, Japan).

## Results

### Background of patients and operative variables

Background of patients and operative variables are shown in Table 1. The majority were female (76.1%), with a median age of 34 years. Median period between the onset of the disease and operation was 16 months. The most frequent indication for operation was intolerance to ATD (41.2%), followed by patient preference (25.4%) and uncontrollable disease (25.4%). Thirty-seven

patients (18.8%) needed preoperative adrenocortical hormone administration due to excessive value of serum free T4 even after potassium iodide intake. Median intraoperative blood loss was 100ml (range: 10-1390) and 4 patients required blood transfusions. The thyroidectomy was carried out by open surgery in 125 patients and VANS in 72. In terms of extent of resection, 137 subtotal thyroidectomies and 60 neartotal/total thyroidectomies were performed. Median weight of thyroid was 45 grams (range: 7-480). While transient hypocalcemia was seen in 19.8% of the patients, permanent hypoparathyroidism only in 1.0%. There was 3.0 % of RLN palsy, all of which were temporary. During study period, we have not experienced hematoma requiring surgical evacuation. The patients were discharged after their operation in median periods of 4 days (range: 2-22).

Factors affecting amount of intraoperative blood loss

Table 2 shows correlation between clinical variables and AIOBL by univariate

analysis. The strongest correlation of AIOBL was found with weight of the thyroid with correlation coefficient of 0.72 ($p<0.0001$). Additionally AIOBL was positively correlated with the period between onset and surgery (correlation coefficient 0.36, $p<0.001$), and negatively with preoperative free T4 at initial consultation (correlation coefficient -0.22, $p<0.01$). The multivariate analysis revealed that only weight of the thyroid was correlated with AIOBL ($p<0.0001$) (Table 3). We show the four patients who needed intraoperative blood transfusion in Table 4. Two out of 4 underwent autotransfusion with preoperatively collected blood.

Impact of intraoperative blood loss on postoperative courses

Although AIOBL was positively correlated with amount of drainage (correlation coefficient 0.47, $p<0.0001$) and duration of drain retained (correlation coefficient 0.25, $p<0.001$), no correlation was seen between AIOBL and postoperative hospital stay (Table 5). Furthermore, occurrence of postoperative morbidity

was not correlated with AIOBL.

## Discussion

Thyroidectomy for GD has been one of the acceptable therapeutic options although prevalence differs from country to country.[1] RI is regarded as safe and effective therapeutic modality; the majority of patients in the United States are treated with RI[1,8] and RI has become a major therapeutic option in Japan. Surgery, however, still plays an important role and thyroidectomy has advantages, such as, a rapid therapeutic effect, a lower recurrence rate than RI or ATD,[8-10] especially, no risk of recurrences after removal of whole gland.[9] Moreover, when ATD is intolerable, surgery is the only possible therapeutic modality in the patient with unwillingness to take RI, with Graves' ophthalmopathy and in pregnancy.[1, 2]

In the present study, huge goiter was only the clinical variable that had positive correlation with AIOBL by multivariate analysis. The thyroid gland in Graves'

patient is rich of vascularity and has dilated vessels around it, and resulted in being prone to bleed from surface of it or surrounding vessels.[5] Additionally, hemostasis should be troubling with huge goiter, due to difficulty in mobilizing thyroid, reaching vasculatures, and subsequently cutting off inflow of blood. We experienced 2 permanent hypoparathyriodism (1.0%) and no permanent RLN palsy postoperatively, whose rates were comparable to previous reports.[2, 9, 11] Since the numbers of patients with these permanent complications were too small to address statistical evaluation, we evaluated transient complications in this study. Among benign goiter surgeries, GD itself was shown as an independent risk factor for either postoperative transient hypoparathyroidism [12] or RLN palsy.[13] In our study, AIOBL was not related to the complications, and that might be the reason why no correlation between AIOBL and postoperative stay.

Continued growth of a Graves' goiter in the patient on ATD and increasing the difficulty of a delayed thyroidectomy was reported.[2] In our analysis, disease

period was positively correlated with weight of thyroid and inversely correlated with free T4 levels by univariate analysis (data not shown). This implied that the indication for thyroidectomy changed with course of the disease, namely, while patients with short term of disease tended to undergo thyroidectomy due to functional issues, those suffering the disease for long term did due to other reasons, such as huge goiter and Graves' ophthalmopathy, even with function being controlled by ATD. Several randomized trial showed that administration of ATD for more than 18 months did not confer improvement of remission rate.[14-16] While Ervis et al. showed negative correlation between ADT treatment duration and AIOBL by multivariate analysis, [17] our result was opposite by univariate analysis even though most of our patients took ATD at the time of operation. The reason of this discrepancy was not defined and, form our results, definitive therapy should be considered after a couple of years of ATD therapy not only from the aspect of remission rate but also the safety on operation.

Four out of 11 cases with thyroid above 200 grams underwent intraoperative blood transfusion (data not shown). We could not evaluate the vascularity, which was reported to affect AIOBL,[17] in all cases because of retrospective study. We believe that further prospective examinations might find notable formula that predicts AIOBL more accurately. Regardless of this limitation, our results recommend the preparation for blood transfusion in the GD patient with huge goiter estimated above 200 grams.

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Table 1

| Background of patients | |
|---|---|
| Age (year-old) | 34.0 (11-74) * |
| Sex, male : female | 47 : 150 |
| Period between disease onset and surgery (months) | 16 (1-480) * |
| Indication for surgery | |
| Intolerance to antithyroid drug | 81 (41.2%) |
| Patient preference | 50 (25.4%) |
| Uncontrollable | 50 (25.4%) |
| Large goiter with pressure symptoms | 41 (20.8%) |
| Poor adherence | 20 (10.2%) |
| Graves' ophthalmopathy | 10 (5.1%) |
| Planned pregnancy | 6 (3.0%) |
| Suspicious of melignancy | 2 (1.0%) |

| | |
|---|---|
| Thyrotoxic crisis | 2 (1.0%) |
| Young age | 1 (0.5%) |
| Failure of RI therapy | 1 (0.5%) |
| Preoperative TSH at initial consultatioin (ng/ml) | 0.005 (0.0-77.6) * |
| Preoperative free T4 at initial consultation (ng/ml) | 2.6 (0.2-21.3) * |
| Preoperative steroid | 37 (18.8%) |
| Preoperative b-blocker | 79 (40.1%) |
| Variables of surgery | |
| During of Surgery (minutes) | 186 (69-380) * |
| Amount of blood loss (ml) | 100 (10-1390) * |
| Blood transfusion | 4 (2.0%) |
| Operative methods | |
| Open surgery : VANS | 125 : 72 |
| Subtotal : Neatotal/total thyroidectomy | 137 : 60 |

| | |
|---|---|
| Weight of thyroid (gram) | 45 (7-480) * |
| Surgical complications | |
| Transient hypocalcemia | 40 (19.8%) |
| Permanent hypoparathroidism | 2 (1.0%) |
| Transient RLN palsy | 6 (3.0%) |
| Permanent RLN palsy | 0 (0.0%) |
| Amount of drainage during initial 6 hours (ml) | 41 (6-114) * |
| Removal of drain (days) | 1 (1-3) * |
| Postoperative hospital stay (days) | 4 (2-22) * |

Abbreviations: VANS, video-assisted neck surgery; RLN, Recurrent laryngeal nerve. * Median (range)

Table 2

| Correlation between clinical variables and intraoperative blood loss (univariate analysis) | | |
|---|---|---|
| *Continuois vabiables (single regression analysis)* | *correlation coefficient* | *p value* |
| Age (year-old) | 0.08 | 0.28 |
| BMI | 0.05 | 0.47 |
| Period between disease onset and surgery | 0.35 | <0.001 |
| Free T4 at initial consultation | 0.22 | <0.05 |
| Weight of thyroid | 0.72 | <0.0001 |
| *Categorical variables (Student t-test)* | *Amount of bleeding* | *p value* |
| Sex | | |
| male | 120 | |
| female | 107 | 0.55 |

| | | |
|---|---|---|
| Operative methods | | |
| Open | 100 | |
| VANS | 110 | 0.1 |
| Type of surgical resection | | |
| Subtotal | 110 | |
| Near total/total thyroidectomy | 86 | 0.51 |
| Weight of thyroid | | |
| <100 grm * | 90 | |
| >100 ≦200 grm** | 257 | *vs**; p<0.05, |
| >200 grm *** | 560 | *vs*** **vs***; p<0.001 |

Abbreviations: VANS, video-assisted neck surgery

Table 3

| Correlation between clinical variables and intraoperative blood loss (multivariate analysis) | | |
|---|---|---|
| *multiple regression analysis* | *95% Confidence Interval* | *p value* |
| Period between disease onset and surgery | -0.52 to 0.25 | 0.48 |
| Free T4 at initial consultation | -12.61 to 3.8 | 0.29 |
| Weight of thyroid | 1.79 to 2.48 | <0.0001 |

Table 4

| Cases with intraoperative blood transfusion | | | | | |
|---|---|---|---|---|---|
| case | Sex/Age (year) | Extent of resection | Weight of thyroid (gram) | Amount of bleeding (ml) | Type of transfusion |
| 1 | female/30 | total | 245 | 550 | auto |
| 2 | male/48 | total | 480 | 1390 | allogeneic |
| 3 | male/23 | subtotal | 369 | 480 | auto |
| 4 | female/53 | total | 324 | 1250 | allogeneic |

Table 5

| Impact of blood loss on perioperative courses | | |
|---|---|---|
| *Continuois vabiables (single regression analysis)* | *correlation coefficient* | *p* |
| Amount of drainage durign initial 6 hours | 0.47 | <0.0001 |
| Duration of drain retained (days) | 0.25 | <0.001 |
| Postoperative hospital stay (days) | 0.05 | 0.48 |
| | | |
| *Categorical variables (Student t-test)* | *Amount of bleeding* | *p* |
| Sugical complications | | |
| Transient hypocalcemia | | |
| yes | 110 | |
| no | 100 | 0.67 |
| Transient RLN palsy | | |
| yes | 80 | |

| | | |
|---|---|---|
| no | 100 | 0.15 |
| Abbreviations: RLN, Recurrent laryngeal nerve | | |