Change of surgical strategy for Graves’ disease from subtotal thyroidectomy to total thyroidectomy: a single institutional experience

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Abstract. The extent of thyroidectomy in Graves’ disease remains controversial. In our institution, long-term euthyroidism without thyroxin replacement therapy has been the aim, and it has long been the standard surgical procedure used to treat Graves’ disease in many institutions, including our hospital. Based on several clinical studies, it was concluded that subtotal thyroidectomy is not suitable as a standard surgical procedure for the treatment of Graves’ disease. In 2009, the surgical strategy for Graves’ disease was changed from subtotal thyroidectomy to total thyroidectomy in our hospital. In this study, how surgical complications have changed after this modification was examined. The subjects were 1,476 patients with Graves’ disease treated by thyroidectomy between 2006 and 2014. There were 1,119 females and 357 males with a median age of 39 years. A total of 660 patients underwent bilateral subtotal thyroidectomy (ST group), and 816 patients underwent total thyroidectomy (TT group). Both transient hypocalcemia and prolonged hypocalcemia were observed significantly more frequently in the TT group than in the ST group (p < 0.001). Total thyroidectomy was identified as a risk factor for prolonged hypocalcemia on multivariate analysis. In conclusion, total thyroidectomy is a reliable and effective therapy for controlling hyperthyroidism in terms of controlling of hyperthyroidism. However, it should be noted that total thyroidectomy resulted in an increased rate of prolonged hypocalcemia. Surgeons should try to reduce the surgical complication rate as much as possible.

Key words: Graves’ disease, Total thyroidectomy, Surgical complications

THYROIDECTOMY has been used as a treatment option for Graves’ disease including antithyroid drug therapy (ATD) and radioiodine therapy. The treatment modalities used vary in different parts of the world. In the United States, ATD are the most common initial treatment modality, followed by RAI when drug therapy fails. RAI is preferred by endocrinologists in the United States, whereas other European and Asian countries favor ATD followed by surgery [1-4]. Thyroidectomy is effective in the management of patients with Graves’ disease, since it provides rapid control of hyperthyroidism with a high cure rate. Two surgical options are available: subtotal thyroidectomy aiming to preserve thyroid function, and total thyroidectomy to ablate thyroid function, eliminating the risk of recurrent hyperthyroidism. Subtotal thyroidectomy is considered the optimal surgical procedure for achieving permanent remission without the need for postoperative medication, and it has long been the standard surgical procedure used to treat Graves’ disease in many institutions, including our hospital. We previously reported that thyroid function after subtotal thyroidectomy was unstable relapse rate of hyperthyroidism was high after subtotal thyroidectomy [5-8]. Thus, we changed the surgical strategy for Graves’ disease from subtotal thyroidectomy to total thyroidectomy in 2009. In this study, how the surgical complications changed after our modification of surgical strategy for Graves’ disease was examined.

Patients and Methods

Between 2006 and 2014, 1,928 patients with Graves’ disease underwent thyroidectomy in our hospital. Excluding 452 patients with associated primary hyperparathyroidism, thyroid carcinoma requiring lymph node dissection, and patients who previously underwent thyroidectomy, the remaining 1,476 patients were the subjects of this study. During this period, 24 endocrine
surgeons were involved, with experience as an endocrine surgeon ranging widely from less than 5 years to more than 20 years. In patients who underwent subtotal thyroidectomy, the remnant thyroid was left widely and thinly to protect the parathyroid glands and the recurrent laryngeal nerves. Thyroid remnants on both sides were estimated by modeling the remnants to the resected segment. The segment was then weighed. By leaving the posterior capsule and thyroid tissue, the recurrent nerves were not exposed, thus avoiding injury to the nerves. An attempt was made to leave all parathyroid glands in situ. In patients treated by total thyroidectomy, the recurrent nerves were identified and preserved, and every effort was made to preserve all parathyroid glands in situ, but whenever a parathyroid gland was resected in patients treated by both subtotal and total thyroidectomy, it was transplanted into the sternocleidomastoid muscle.

Common surgical complications of subtotal thyroidectomy for Graves’ disease are hypocalcemia (hypoparathyroidism), hoarseness (recurrent laryngeal nerve palsy), and bleeding requiring re-operation. The serum calcium, phosphate, and albumin levels of all patients were measured on the day after thyroidectomy. Hypocalcemia was diagnosed and evaluated on the basis of a physical examination and serum calcium determination. Postoperative hypocalcemia was managed by oral administration of vitamin D3 and/or calcium supplementation. Transient hypocalcemia is defined as recovery of parathyroid function within six months after surgery, and prolonged hypocalcemia is defined as the need for oral vitamin D3 and/or calcium supplementation to maintain serum calcium normal for more than 6 months after surgery. With respect to postoperative vocal cord function, the vocal cords were not evaluated by laryngoscopy before and after surgery in the earlier series of patients. Thus, incidence of vocal cord dysfunction as a surgical complication was excluded from this study. Postoperative bleeding was managed surgically if progressive swelling of the neck was noted.

Descriptive analyses were performed using JMP 12.0 (SAS Institute, Inc., Cary, NC, USA). Differences between proportions were tested by Chi-squared test, and between means by using Student’s *t* test. For multivariate analysis, logistic regression was used to assess the risk factors for surgical complications. The included variables were sex, age, extent of thyroidectomy, amount of blood loss during surgery, and weight of the resected thyroid gland. A *p* value <0.05 was considered significant.

The protocol of this study was reviewed and approved by the Institutional Review Board, and the study was performed in accordance with the Declaration of Helsinki.

Results

Patients’ characteristics

There were 1,119 females and 357 males, with a median age of 39 years (range: 9 to 80 years). A total of 660 patients underwent bilateral subtotal thyroidectomy (ST group) and 816 patients underwent total thyroidectomy (TT group). Patients’ characteristics in both groups are shown in Table 1. There was no significant difference in the sex ratio between the groups. TT group patients were significantly older and had larger goiters than ST group patients. Though operation time was significantly longer in the TT group patients, hemorrhage volume during surgery was significantly lower in TT group patients. Thirty-three patients (5.0%) in the ST group and 400 (49.0%) patients in the TT group had one or more parathyroid glands auto-transplanted during surgery. Significantly more TT group patients than ST group patients had 2 or more auto-transplanted parathyroid glands (*p* < 0.001). Annual ratio of patients with subtotal thyroidectomy and total thyroidectomy were shown in Table 2. At the middle of 2009, we changed surgical strategy for Graves’ disease, but both before and after 2009, several patients chose and underwent different procedure that we recommended.

Surgical outcomes and complications

With a median follow-up of 165 months after thyroidectomy, 477 patients (72.3%) had hypothyroidism, 68 patients (10.3%) had recurrent hyperthyroidism, and only 115 patients (17.4%) had euthyroidism in the ST group. All TT group patients had hypothyroidism requiring thyroxin replacement therapy.

The comparison of surgical complication rates between TT group patients and ST group patients is shown in Table 3. There was no significant difference between the groups in the incidence of postoperative bleeding requiring re-operation. Both transient and prolonged postoperative hypocalcemia occurred significantly more in TT group patients than in ST group patients (*p* < 0.0001). Annual incidences of postoperative hypocalcemia and bleeding were shown in Table 2. Incidence of surgical complications was almost same in each year. Most TT group patients with postoperative hypocalcemia had transient hypocalcemia, but significantly more patients with prolonged hypocalcemia were observed in the TT group than in the ST group. Five TT group patients with prolonged hypocalcemia recovered from hypocalcemia from 2.5 to 3 years after thyroidectomy, and hypocalcemia continued in the other 37 patients with a median follow-up of 3.5 years after surgery. However, 22 (50%) of these 44 patients with prolonged hypocalcemia had normal intact PTH (3 in the ST group and 19 in the TT group).
Patients with hypocalcemia in the TT group included 34 of 416 patients without auto-transplanted parathyroid glands (8.2%), 9 of 251 patients with one auto-transplanted parathyroid gland (3.6%), and 9 of 149 patients with more than 2 auto-transplanted parathyroid glands (6.0%). The rate of prolonged hypocalcemia was not significantly different among these 3 groups. In patients with prolonged hypocalcemia, average dose of vitamin D3 to maintain their serum calcium normal was 1.5 μg ranging from 0.25 to 4 μg. In average dose to maintain their serum calcium normal, patients after subtotal thyroidectomy took orally 1.8 μg vitamin D3 and patients after total thyroidectomy took orally 1.4 μg vitamin D3, which was no significant difference between them. The results of univariate and multivariate analyses for prolonged hypocalcemia are shown in Table 4. Both univariate and multivariate analyses showed that total thyroidectomy was the significant risk factors for prolonged hypocalcemia.

**Discussion**

Formerly, young patients, especially child-bearing-aged females, often underwent thyroidectomy in our hospital. However, recently, radioiodine therapy for young patients has been widely accepted, and this has resulted in a decreased number of patients undergoing thyroidectomy. Remission is rarely achieved in Graves’ patients with large goiters by medical therapy, and several courses of radioiodine therapy are necessary to achieve remission. In our hospital, the percentage of patients treated surgically has tended to decrease gradually, and medical
therapy has become the mainstream treatments for Graves’ disease in recent years, while surgery has been used to treat about 5% of the patients [8]. Surgery still has several advantages, and it has not been completely abandoned.

The controversy regarding the extent of thyroidectomy in Graves’ disease still continues [9-15]. The main purpose of surgical management for Graves’ disease is relief from hyperthyroidism, but the extent of thyroidectomy is decided by the balance of the risks of disease relapse, lifelong thyroid hormone replacement therapy, and the rate of postoperative complications. The guidelines for the management of hyperthyroidism published by the American Thyroid Association of Clinical Endocrinologists [2] recommend total thyroidectomy as a standard surgical procedure. On the other hand, subtotal thyroidectomy is chosen in many countries, especially outside the United States and European countries, because of limited access to thyroid hormone replacement therapy. In our hospital, long-standing euthyroidism without medication has been considered the ideal goal of surgical treatment, and subtotal thyroidectomy has been used as a standard surgical procedure for a long time. We have reported the surgical outcomes and the factors related to postoperative thyroid dysfunction, especially recurrent hyperthyroidism [5, 6], and we concluded that there is no more powerful factor than thyroid remnant size related to postoperative thyroid dysfunction. To determine the appropriate size of the thyroid remnant, we prospectively decreased the size of the remnant thyroid [7]. A decreased number of recurrent hyperthyroid patients was achieved, but this also resulted in an increase of hypothyroid patients and a decrease of euthyroid patients. Following these outcomes, we decided to change our surgical strategy for patients with Graves’ disease from subtotal thyroidectomy to total thyroidectomy in 2010.

Regardless of the extent of thyroidectomy, the occurrence of surgical complications has been reported to some extent, and this is why it is usually recommended that thyroidectomy be performed by experienced endocrine surgeons. In our experience, increased surgical complications, especially hypocalcemia, were observed in patients with total thyroidectomy. Several randomized, controlled studies [16-18] showed that significant differences were not observed in surgical complication rates, except transient hypocalcemia, between total thyroidectomy and subtotal thyroidectomy. Surgeon experience cannot be excluded as a reason explaining why postoperative hypocalcemia was more frequently observed in patients with total thyroidectomy. Several papers reported that thyroid surgery is associated with a higher risk for complications when performed by less experienced surgeons [19, 20]. In the present study, the complication rate by surgical experience for Graves’ disease was not examined because the experience of each surgeon at our hospital could be confirmed, but their experiences at hospitals where they previously worked could not be clearly determined.

### Table 3 Surgical complications

<table>
<thead>
<tr>
<th></th>
<th>ST (n = 660)</th>
<th>TT (n = 816)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>15 (2.3%)</td>
<td>20 (2.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Transient Hypocalcemia</td>
<td>100 (15.2%)</td>
<td>224 (27.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prolonged Hypocalcemia</td>
<td>7 (1.1%)</td>
<td>42 (5.1%)</td>
<td>&lt;0.0001</td>
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</table>

NS, not significant

### Table 4 Risk factor analysis for prolonged hypocalcemia

#### Univariate analysis

<table>
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<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p</th>
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<tbody>
<tr>
<td>Age (year)</td>
<td>1.00</td>
<td>0.98-1.02</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>1.95</td>
<td>0.92-4.78</td>
<td>NS</td>
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<tr>
<td>Procedure (TT)</td>
<td>5.06</td>
<td>2.41-12.39</td>
<td>&lt;0.0001</td>
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<tr>
<td>Op time (min)</td>
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<td>0.99-1.00</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding amount (g)</td>
<td>1.00</td>
<td>0.99-1.00</td>
<td>NS</td>
</tr>
<tr>
<td>Resected thyroid (g)</td>
<td>1.00</td>
<td>0.99-1.00</td>
<td>NS</td>
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#### Multivariate analysis

<table>
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<th></th>
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<tr>
<td>Age (year)</td>
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<td>0.89-4.80</td>
<td>NS</td>
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<td>Gender (Female)</td>
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<td>Procedure (TT)</td>
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<td>&lt;0.0001</td>
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<tr>
<td>Op time (min)</td>
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<td>0.99-1.02</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding amount (g)</td>
<td>1.00</td>
<td>0.99-1.00</td>
<td>NS</td>
</tr>
<tr>
<td>Resected thyroid (g)</td>
<td>1.00</td>
<td>0.99-1.00</td>
<td>NS</td>
</tr>
</tbody>
</table>

TT, total thyroidectomy; CI, confidence interval; OP, operation
Hypocalcemia after thyroidectomy was observed in some patients with normal PTH levels, and several factors related to hypocalcemia with normal PTH were reported [21, 22]. Twenty-two (50%) of 44 patients with prolonged hypocalcemia had normal intact PTH after surgery, but they all had to take small amounts of vitamin D3 to maintain their serum calcium levels within the normal range. A normal serum PTH level in patients after thyroidectomy does not always mean normocalcemia, and this is why we focused on serum calcium level in the present study. Long standing hyperthyroidism is known to induce hungry bone syndrome and may play a role to the reduction of postoperative PTH response.

There are some limitations in the present study, including the above-mentioned issue of surgeon experience. One of the limitations was that we did not evaluate postoperative vocal cord dysfunction. Postoperative recurrent nerve paralysis is one of important surgical complications but not all patients underwent vocal cord examination by laryngoscopy in the early series of this subject. We now perform vocal examination by laryngoscopy for all patients both before and after thyroidectomy, but not all patients underwent vocal cord examination by laryngoscopy before. Thus, an objective evaluation of the recurrent laryngeal nerve could not be analyzed.

In conclusion, thyroidectomy is a reliable and effective therapy for controlling hyperthyroidism. Subtotal thyroidectomy is proved to be inappropriate because the ratio of euthyroid patients is lower than expected, thyroid function after subtotal thyroidectomy is unstable and life-long follow-up by thyroid specialists is necessary. On the other hand, the fact that no patients experienced recurrent hyperthyroidism after total thyroidectomy is a matter of special mention. All patients are stably euthyroid with medication and most of the patients can be followed by their primary care physicians. In terms of controlling postoperative thyroid function, total thyroidectomy is a surgical treatment of choice. But, it should be focused on that incidence of surgical complication, especially postoperative hypocalcemia, was significantly increased after the change of surgical procedure. Postoperative hypoparathyroidism is mainly related to surgical technique and surgeon’s experience. Improvement of this surgical complication incidence is usually achieved only by training surgical skills. Every surgeon specialized in any fields, learns to reduce their surgical complication rate. We don’t think that increase of prolonged hypocalcemia discourages to recommend total thyroidectomy for Graves’ disease as a standard procedure. However, when total thyroidectomy is selected as a surgical procedure, incidence of prolonged hypocalcemia may increase in every hospital and every surgeon should be trained surgical skill as well.

References

12. Feliciano DV, Lyons JD (2011) Thyroidectomy is optimal


