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The effect of anti-thyroid drug treatment duration and predictive for intraoperative blood loss in patients with Graves' disease

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***Abstract*---**Background: Grave's disease frequently results in and is the most common cause of hyperthyroidism. It also often results in an enlarged thyroid. It also known as toxic diffuse goitre, is an autoimmune disease that affects the thyroid. Objective: To evaluate all the factors that cause intra-operative blood loss and how it affects the grave's disease. Methods: This study was conducted on 200 patients with Grave's disease, who underwent thyroidectomy during the period from May 2010 to April 2016. For a period of 14 days, all patients were administered with potassium iodide before the surgery. Conventional open surgery or neck surgery video assisted were performed. SPSS (Version 22.0) was used for analysis. Results: The majority of patients were females which constitute about 76.3% with a median age of 32 years. The median period between the onset of the disease and operation was 15 months. Weight of thyroid in grams was 40. Post-operative hospital stay was 3 days. Univariate analysis revealed that the strongest correlation of amount of intraoperative blood loss (AIOBL) was noted with the weight of thyroid ($p<0.001$). Additionally, AIOBL was correlated positively with the period between disease onset and surgery ($p<0.001$) and negatively with

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preoperative free T4 ($p<0.01$). Occurrences of postoperative complications, such as recurrent laryngeal nerve palsy or hypoparathyroidism, and postoperative hospital stay were not correlated with AIOBL. Conclusion: For Grave's disease, for excessive bleeding during surgery, a large goitre presented as a predictive factor, and transfusion of blood should be considered in cases in which goitre weighs more than 200 g.

***Keywords*---**goitre, hyperthyroidism, Graves' disease, thyroidectomy, autoimmune thyroiditis, radioisotope iodine, hypocalcemia.

Introduction

Graves' disease (GD) is an autoimmune disease, in which thyroid-receptor antibodies combine with the thyrotropin receptor, promoting the production of thyroid hormones in the follicular cells through stimulation of cyclic adenosine monophosphate.[1] The condition is named after Robert Graves, who described it in 1835. The exact cause is unclear; however, it is believed to involve a combination of genetic and environmental factors. While a theoretical mechanism occurs by which stress could cause an aggravation of the autoimmune response that leads to Graves' disease, more robust clinical data are needed for a firm conclusion. The three treatment options are radioiodine therapy, medications, and thyroid surgery. Radioiodine therapy involves taking iodine-131 by mouth, which is then concentrated in the thyroid and destroys it over weeks to months. [2] The resulting hypothyroidism is treated with synthetic thyroid hormone. Medications such as beta blockers may control some of the symptoms, and antithyroid medications such as methimazole may temporarily help people while other treatments are having effect. Surgery to remove the thyroid is another option. Eye problems may require additional treatments. Graves' disease will develop in about 0.5% of males and 3% of females.[3,4].Nevertheless, suspicion of malignancy, unwillingness to receive RI therapy, and pregnancy should still be good indications for surgery. Although thyroidectomy has been regarded as a prompt and assured therapy for GD, it has some drawbacks, such as operative scar, need for hospitalization, and complications related to operation, including recurrent laryngeal nerve (RLN) paralysis, hypoparathyroidism, and intraoperative bleeding.[5]Thyroidectomy is considered as a prompt therapy for Grave's disease but it has few disadvantages such as scar post operatively, need for hospitalization, operation complications, recurrent laryngeal nerve, hypoparathyroidism, and intra-operative bleeding. This study evaluates all the factors that cause intra-operative blood loss and how it affects the grave's disease.

Materials and Methods

This study was conducted on 200 patients with Grave's disease, who underwent thyroidectomy during the period from May 2018 to April 2022 in a tertiary care hospital. The excluded patients were those who had undergone neck surgery before. For a period of 14 days, all patients were administered with potassium iodide before the surgery. Conventional open surgery or neck surgery video assisted were performed.GD was defined by the presence of thyrotoxicosis, a

diffuse goitre, and a serum thyroid-stimulating hormone receptor antibody or thyroid-stimulating antibody. After the operation, the diagnosis was confirmedhistologically in all patients. In preparation for surgery, all patients were given potassium iodide for a median period of 14 days. Operations were performed with conventional open surgery or video-assisted neck surgery. The indications and technique of video-assisted neck surgery were described previously.[6]Subtotal thyroidectomy was defined as leaving between 2 g and 6 g thyroid tissue and near-total thyroidectomy was defined as leaving <2 g thyroid tissue.

Methodology

We placed closed suction drainage tubes prior to wound closure in all of the patients except one and removed them 1-3 days later. RLN injury was recorded if voice change was recognized. Calcium supplements and vitamin D analogswere given to those with symptomatic hypocalcemia. Patients who could discontinue the supplements after achieving normocalcemia within 12 months after surgery were identified as those with transient hypocalcemia, whereas patients who had to continue it for more than 12 months and continued to have a below-normal serum intact parathyroid hormone level were categorized as those with permanent hypoparathyroidism. The study was approved by Institutional Ethics Committee.

Statistical Analysis

The recorded observation were collected in Microsoft excel sheet and exported to SPSS (Version 22.0) for analysis. Univariate analysis was performed by single regression analysis to test the correlation between continuous variables and AIOBL, and Student t test was used to compare between groups. A p value of <0.05 was considered statistically significant. For multivariate analysis, p value of ≤ 0.10 was considered to be stepwise regression analysis to determine the risk factors for intra-operative bleeding.

Results

Table 1- Demographic details and Indication of Surgery and Operative variables

Indicationforsurgery	N(%)
Age in years	32(10-70)
Male:female ratio	48:152
Intolerancetoantithyroiddrug	81 (40)
Patientpreference	46 (22.5)
Uncontrolledisease	45 (22.5)
Largegoitrewithpressuresymptoms	41 (20)
Pooradherence	14(7.5)
Grave'sophthalmology	10(5)
Plannedpregnancy	5 (2.5)
Malignancysuspicion	1 (0.5)
Thyrotoxiccrisis	1 (0.5)
Young age	1 (0.5)

Failureofradioiodinetherapy	1 (0.5)
Pre-operativesteroid	35 (17.5)
Pre-operativeβ-blocker	80 (40)

As per table 1 the majority of patients were females which constitute about 76.3% with a median age of 32 years. Among the indications of surgery around 40% has intolerance to antithyroid medications found to be most common indication. 23% has uncontrollable disease other indication are large goitre, uncontrolled disease, poor adherence. Weight of thyroid in grams was 40. Post-operative hospital stay was 4 hours.

Table 2- Operative Methods and Surgical Complications

Variable	Values
Operativemethods	
Opensurgery:videoassistednecksurgery	130:70
Subtotal:neartotal/totalthyroidectomy	145:55
Surgicalcomplications	N(%)
Transienthypocalcemia	35 (19)
Permanenthypoparathyroidism	1 (0.5)
Transientrecurrentlaryngealnervepalsy	5 (2.5)
Permanentrecurrentlaryngealnervepalsy	0 (0.0)

As per table 2 open surgery video assisted neck surgery was the most common option in more than 50% of patients. Followed by total or near total thyroidectomy. The most common surgical complication was hypocalcemia in 19% of patients.

Table 3- Univariate analysis for Correlation between clinical variables and intra-operative blood loss

Variable	Correlation coefficient	P value
Continuousvariables		
Age in years	0.06	0.15
BMI	0.04	0.43
Periodbetween disease onset and surgery	0.34	0.01
FreeT4 atinitial consultation	0.20	0.01
Weight ofthyroid	0.70	0.001
Categoricalvariables		
Sex		0.51
Operativemethods		0.13
Typeof surgicalresection		0.50

As per table 3 all the continuous variables shows positive correlation but significance was seen with duration of disease, weight of thyroid, free t4

consultation. Categorical variables like sex, operative methods are not statistically significant. ($p>0.05$).

Discussion

Thyroidectomy for GD has been one of the acceptable therapeutic options, although its prevalence differs from country to country.[1]RI therapy is regarded as a safe andeffective therapeutic modality; the majority of patients inthe United States are treated with RI therapy,[1]which has become a major therapeutic option in India as well. Surgery, however, still plays an important role, and thyroidectomy has certain advantages, such as a rapid therapeutic effect, a lower recurrence rate than RI therapy or ATDs,[8]and especially no risk of recurrence after the removal of the whole gland.[7]Moreover, when ATDs are intolerable, surgery is the only possible therapeutic modality in patients who are unwilling to receive RI therapy, have Graves'ophthalmopathy, and are pregnant.[1,2]

Yamanouchi et al reported that a total of 197 patients underwent thyroidectomy for Graves' disease between 2002 and 2012.[9]it was evaluated those clinical factors that would be potentially related to AIOBL retrospectively. The median period between disease onset and surgery was 16 months (range: 1-480 months). Conventional surgery was performed in 125 patients, whereas video-assisted surgery was performed in 72 patients. Subtotal and near-total/total thyroidectomies were performed in 137 patients and 60 patients, respectively. The median weight of the thyroid was 45 g (range: 7.3-480.0 g). Univariate analysis revealed that the strongest correlation of AIOBL was noted with the weight of thyroid ($p<0.001$).Occurrences of postoperative complications, such as recurrent laryngeal nerve palsy or hypoparathyroidism, and postoperative hospital stay were not correlated with AIOBL. Grodski et al, conducted a study in which the most frequent absolute indication was the presence of a large goitre (n=8; 13%) or associated thyroid nodule (n=6; 10%)[6]Ophthalmopathy, a relative indication, comprised the largest single group overall (n=18; 29%); however, a significant number of patients (n=17; 27%) elected surgery in the absence of a recognized indication.Erbil et al reported that the mean blood flow, MVD, CD-34 expression, and blood loss in group 1 patients were significantly lower than those in group 2 patients.[10]

Multivariate logistic regression analysis showed that extended resection (OR-odds ratio-1.6), Graves' disease (OR 2.7), thyroiditis (OR 2.1), recurrent goitre (OR 2.3) and thyroid malignancy (OR 1.7) were all independent risk factors for transient RLNP, whereas Graves' disease (OR 2.2) and recurrent goitre (OR 1.7) emerged as independent risk factors for permanent RLNP. The rates of transient and permanent hypopara-thyroidism were 27.8% and 4.8%, respectively. Multivariate analysis for transient hypoparathyroidism revealed that the extent of surgical resection (OR 2.2), Graves' disease (OR 2.1), recurrent goitre (OR 1.7), female gender (OR 1.5) and specimen weight (OR 1.6) was independent predictors. However, the extent of surgical resection (OR 2.7), Graves' disease (OR 1.8), recurrent goitre (OR 1.5) and malignant disease (OR 1.5) were independent risk factors for permanent hypoparathyroidism. Postoperative wound infection and hematoma occurred in 6 (0.3%) and 27 (1.3%) patients, respectively.[10,11] No

correlation was observed between wound infection or postoperative hemorrhage and the extent of surgery.

Allannic et al performed a prospective randomized study was performed in patients with hyperthyroid Graves' disease (GD) in order to compare long (18 months) and short term (6 months) antithyroid drug treatment on the remission rate.[11] A therapeutic protocol was offered to all GD patients who had not been treated for this disease previously Of the patients having undergone long term treatment, 61.8% still were in remission 2 year after treatment withdrawal, whereas only 41.7% of the patients treated for 6 months were in remission (P less than 0.05). Such findings clearly establish that treatment duration has a direct beneficial incidence on the remission rate.[12]

Conclusion

A huge goitre presented as a predictive factor for excessive bleeding during surgery for Graves' disease, and preparation for blood transfusion should be considered in cases where thyroids weigh more than 200 g.

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Conflict of Interest- None declared

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