Comparison of urgent and elective thyroidectomy complications in Graves' disease

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BACKGROUND: *Surgical treatment of Graves' disease (GD) has increased risk for bleeding, hypothyroidism and recurrent laryngeal nerve (RLN) palsy compared to other benign thyroidectomy indications. Nevertheless, it can be done safely in high volume centers. In some particular cases (i.e., anti-thyroid drug intolerance or thyrotoxicosis), urgent surgical treatment might be needed. In this study, we aimed to compare the complications of thyroidectomy in urgent and elective management of Graves' disease.*
METHODS: *The patients, who underwent total thyroidectomy due to Graves' disease between 2012-2019 (n=113) were evaluated retrospectively in terms of demographics, pre-operative laboratory results, management, hospital admissions, operative and post-operative short-term outcomes, morbidity and mortality. Patients who were hospitalized to endocrinology department due to uncontrollable hyperthyroidism and related complications and who were prepared for surgery with Lugol's solution, plasmapheresis and steroids were considered as Urgent Group (n=12). Remaining 101 patients who underwent elective surgery considered as Elective Group. Surgical short-term outcomes, morbidity and mortality rates were compared.*
RESULTS: *Of the 113 patients who were operated for GD, 92 were female and 21 were male. In urgently operated group, FT4 and FT3 levels were significantly higher (p<0.001 and p=0.001, respectively). There was no significant difference in transient or permanent hypocalcemia (p=0.821 and p=0.501, respectively), transient or permanent RLN palsy (p=0.356, p=0.634, respectively) and post-operative bleeding (p=0.338), between elective surgery and rapid optimization groups.*
CONCLUSION: *Emergency surgery for Graves' disease can be performed safely with the application of effective pre-operative treatment protocols.*

KEY WORDS: Graves' Disease, Thyroidectomy complications, Urgent thyroidectomy

Introduction

Graves' disease (GD) represents 50-80% of all patients with hyperthyroidism. Although it can be seen at any

age, its frequency increases between the ages of 40-60 and it is seen 5 times more in women [1].
The main goal of treatment is to normalize thyroid hormone levels and achieve remission. There are three different treatment modalities in the treatment of GD; anti-thyroid drug (ATD), radioactive iodine ablation (RAI) and surgery. ATD's are usually the first step of treatment for 6-18 months [2]. Following this treatment, 30-40% relapse is observed [3]. If medical therapy fails to succeed, definitive treatment with either surgery or RAI is considered. Surgery is preferred in patients who are

pregnant, unsuitable for RAI or those with severe eye disease or large goiters [4]. However, potential complications such as recurrent laryngeal nerve (RLN) injury and hypoparathyroidism rates are higher during surgery for GD than other benign thyroid diseases [5].

Preoperative preparation of patients is important to avoid thyroid storm caused from leakage of thyroid hormones to the peroperative circulation and to reduce postoperative complications [6]. In patients with uncontrolled disease, who need urgent surgery, rapid pre-operative preparation may be necessary [7]. There are different modalities in use. Frequently preferred treatment modalities are as follows: ATD, steroid and ß-blockers, Lugol's solution, lithium and plasmapheresis [7,8]. ATD's block the production of thyroid hormone from the gland, ß-blockers can control the peripheral effects of thyroid hormones, and also decrease conversion of T4 to T3. Lugol's solution inhibits thyroid hormones' organification by the Wolff–Chaikoff effect [9]. Glucocorticoids reduce T4 to T3 conversion [9]. Cholestyramine binds to iodothyronines in the gastrointestinal tract and prevents absorption [10]. Thyroid hormones are bound to plasma proteins by 99%, and these proteins are removed by plasmapheresis. However, plasmapheresis is an invasive procedure and it also has severe complications [11].

There is an explanation at the top (RLN) injury, hematoma and hypoparathyroidism are known complications of thyroidectomy which are higher in the setting of GD than other benign thyroid diseases [5]. Chronic inflammation and increased vascularity are major causes of increased morbidity in thyroidectomy of GD patients [12]. In this study, we aimed to compare the postoperative results of uncontrolled GD patients who underwent urgent surgery after rapid preparation and well controlled GD patients who underwent elective surgery.

Methods And Material

The patients, who underwent total thyroidectomy due to Graves' disease between 2012-2019 (n=113) in our department were evaluated retrospectively in terms of demographics, pre-operative laboratory results, pre-operative outpatient clinic and hospital admission notes, operative and post-operative short-term outcomes, morbidity and mortality. Study flowchart is shown at Fig. 1.

Patients who were admitted to the endocrinology department due to uncontrollable hyperthyroidism and related complications and prepared for surgery with Lugol's Iodine, plasmapheresis and steroids were considered as Urgent Group (n=12). Remaining patients who underwent elective surgery were considered as Elective Group (n=101). Surgical short-term outcomes, morbidity and mortality rates were compared.

The vocal cord (VC)examination was performed preoperatively for for all patients and postoperative day 1 for patients who have a voice change or hoarseness using a

flexible laryngoscope by an otolaryngologist. Patients who were diagnosed with RLN paralysis in the postoperative period underwent an additional VC examination at 1, 2, 4, and 6 months. RLN paralysis and hoarseness that continued more than 6 months was accepted as permanent paralysis. Patients with a postoperative calcium level <8 mg/dL were recorded as transient hypocalcemia. Patients who needed replacement therapy longer than 6 months and/or whose serum parathyroid hormone level was <15 pg/mL after 6 months were evaluated as permanent hypocalcemia.

This study was carried out in accordance with the 1964 Helsinki Declaration and its recent amendments. Consents were obtained from conscious patients and from first degree relatives in unconscious patients. Ethical approval was obtained from the local ethics committee (Ref. Nr: 2020-02-10)

PRE-OPERATIVE MANAGEMENT PROTOCOL FOR URGENT GROUP

Urgent thyroidectomy was planned in patients with uncontrolled GD (persistent hyperthyroidism while taking high dose ATD treatment, moderate to severe Graves' ophthalmopathy, enlarged goiter, non-compliance to ATD) and ATD associated major side effects (agranulocytosis, small-vessel vasculitis, hepatotoxicity). Lugol's solution (7 drops, 8mg iodide/drop) three times daily, cholestyramine and dexamethasone treatment was preferred in patients with mild hyperthyroidism, while plasmapheresis was used in patients with moderate-severe
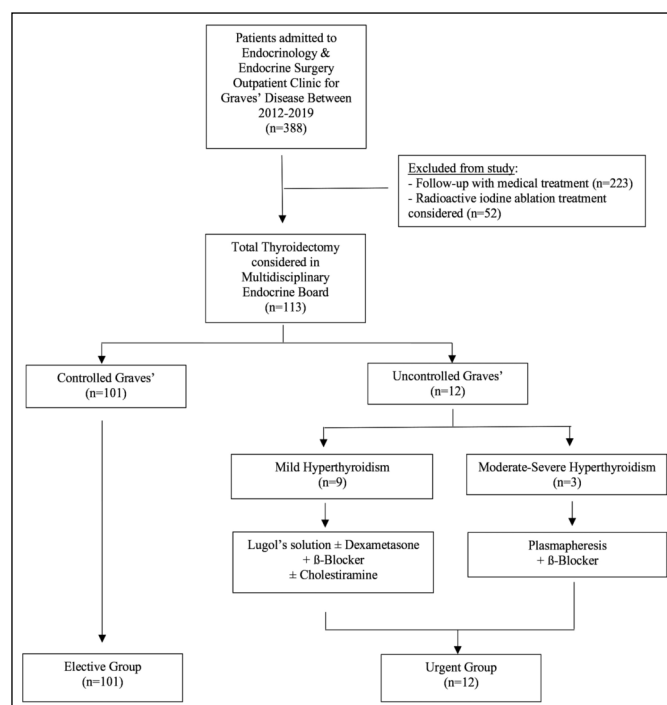

Fig. 1: Study Flowchart.

hyperthyroidism for preparing urgent surgery. ATD treatment was also continued in patients without serious ATD associated side effects (agranulocytosis, vasculitis). ß-adrenergic blockade treatment was given to all patients (Fig. 1).

STATISTICAL ANALYSIS

Statistical software (JMP® version 9.0.1, SAS®, Cary, NC) was used for the statistical analysis. Continuous variables were given as mean±SD values or median and interquartile ranges and categorical variables were given as frequencies and percentages. The Chi-square test was used when comparing the categorical variables. Student's T-test was used for the comparison of parametric continuous variables and Mann-Whitney U test was used for comparison of nonparametric variables. P values of 0.05 or below were accepted as statistically significant.

Results

Of the 113 patients who were operated for GD, 92 were female and 21 were male. 101 patients were well controlled and had elective surgery. All patients underwent total thyroidectomy. There was no statistically significant difference in age (p=0.759) and gender (p=0.559) between urgent and elective groups. Also, there was no difference in terms of ophthalmopathy (p=0.272) in both groups. Nodule formation was observed in 41 patients in the elective and 1 patient in the urgent group (p=0.005). In the elective group, 33 patients had benign (Bethesda 2) fine needle aspiration biopsy (FNAB) results, while in the emergency group, one patient had benign FNAB, eight patients in the elective group had suspicious (>Bethesda 3) findings (p=0.003), (Table I). Three patients in the elective group had a previous thyroid surgery. Mean propylthiouracil (PTU) and methimazole (MMZ) dosages were significantly higher in the urgent group (p=0.023 and p <0.0001, respectively). In the urgent group; 7 patients had leukopenia, 4 patients had severe liver enzyme elevation and 1 patient had vasculitis as ATD side effects (Fig. 2). The mean duration of hospitalization in urgent group was 8 days. There was no significant difference in elective (25.5±2.1 months) and urgent (30.3±7.6 months) groups in terms of mean duration of medical treatment (p=0.468). The mean FT4, FT3 and TSH levels on emergency admissions were 3.2 ng/dL, 13.3 pg/dL, 0.01 mIU/L respectively, for the urgent group. All patients (n=113) underwent total thyroidectomy (Figure 3). The demographics and clinical features of patients are shown in Table I.

In the urgent group, 6 patients received Lugol's solution, 3 patients received plasmapheresis, 2 patients received steroids and one patient received steroid+Lugol's solution treatment regimen. In the urgent group, pre-
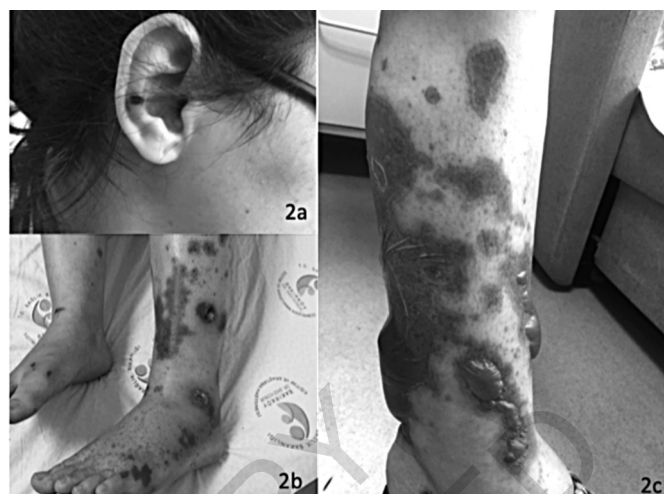

Fig. 2: Clinical Findings of PTU associated vasculitis in a patient with Graves' Disease. Ear involvement (2a), Early stage leg involvement (2b), Late stage leg involvement of the same patient (2c).

operative T4 and T3 levels were significantly higher (p<0.001 and p=0.001, respectively). There was no significant difference in transient or permanent hypocalcemia rates (p=0.821 and p=0.501, respectively). Also, transient or permanent RLN palsy (p=0.356, p=0.634, respectively) and post-operative bleeding rates (p=0.338) were similar. There was no difference in postoperative calcium levels in both groups (p=0.669). The perioperative outcomes of patients are shown in Table II. Micro focal tumor focus was detected in 1 of the 33 patients evaluated as benign by FNAB. In addition, classical variant papillary thyroid carcinoma was detected in a patient whose FNAB result was Bethesda 4. Thus, FNAB and final histopathology were incompatible in 2 patients (Table II). Final histopathology was reported as benign in 92% of patients (n=104) with microscopic features of hyperfunctioning gland (Fig. 4). Micro focal tumor was detected in 1 of the 33 patients evaluated as benign by FNAB. In addition, classical variant papillary thyroid carcinoma was detected in a patient whose FNAB result was Bethesda 4. Thus, FNAB and final histopathology were inconsistent in 2 patients (Table II).

Discussion

The most common cause of hyperthyroidism is GD and thyroidectomy is the most effective definitive treatment in Graves' Disease [8,13,14]. The indications for surgery in GD are; presence of orbitopathy, pregnancy, suspected thyroid malignancy, large thyroid nodule, coexisting primary hyperparathyroidism and a contraindication for ATD and RAI [9,15,16]. This study demonstrates that the outcomes following elective surgery in well-controlled disease and urgent surgery after rapid pre-operative optimization of thyroid complications are parallel.

TABLE I - *Demographics and clinical features of patients.*

Parameter	Elective Group (N=101)	Urgent Group (N=12)	P Value
Age, years, median (IQR)	40 (15-70)	39.5 (21-64)	0.759
Gender, n (%)			
Female	83 (82.2)	9 (75)	0.559
Male	18 (17.8)	3 (25)	
Orbitopathy, n (%)			
(-)	67 (66.3)	6 (50)	0.272
(+)	34 (33.7)	6 (50)	
Nodule formation, n (%)			
(-)	54 (53.5)	11 (91.7)	0.005
(+)	47 (46.5)	1 (8.3)	
*FNAB, n (%)			
No nodules found	60 (59.4)	11 (91.7)	0.003
Benign (Bethesda 2)	33 (32.7)	1 (8.3)	
Suspicious (>Bethesda 3)	8 (7.9)	-	
Previous thyroid surgery, n (%)	3 (2.9)	-	0.408
Medication, n (%)			
**PTU	16 (15.8)	9 (75)	0.0001
†MMZ	68 (67.3)	3 (25)	
Mean time of medication, months (Mean±SD)	25.5±2.1	30.3±7.6	0.468
Mean dosage, mg (Mean±SD)			
PTU	161.5±31.6	333.4±57.2	0.023
MMZ	17.5±1.6	58.3±7.9	<0.0001
Drug related complication, n (%)			
Leucopenia	-	7 (58.4)	N/A
Severe increase of liver enzymes	-	4 (33.3)	
Vasculitis	-	1 (8.3)	
Emergency Hospitalization to Endocrinology, day (Mean±SD)	-	8.1±1.9	N/A
Lab values on emergency admission (Mean±SD)			
‡FT3 (pg/mL)	-	13.3±3.7	
‡FT4 (ng/dL)	-	3.2±0.8	N/A
§TSH (IU/mL)	-	0.01±0.005	

*FNAB: Fine Needle Aspiration Biopsy, **PTU: Propylthiouracyl, †MMZ: Methimazole, ‡FT3/4: Free T3/4, §TSH: Thyroid-Stimulating Hormone

In this study, female gender (n=92) is predominant in both groups, in accordance with the literature [17] and there was no statistically significant difference in age (median of 40 vs. 39.5 years) between urgent and elective groups. Almost half of patients with GD develop Graves' ophthalmopathy (GO), an inflammatory eye disease caused by the cross-reactivity of antibodies to the TSH receptors that are also found on retro-ocular fibroblasts and adipocytes [18]. Thyroidectomy is recommended in patients with GO [19,20]. In our study, there was no significant difference in ophthalmopathy between the urgent and elective groups (p=0.272).

In Graves' patients, the prevalence of palpable thyroid nodules is approximately three times greater than in the general population [21]. In the present study, nodule formation was observed in 47 patients in the elective and 1 patient in the urgent group (p=0.005). FNAB is the recommended method to evaluate thyroid nodules, when necessary in patients following thyroid ultrasonography [22]. Several studies have demonstrated an increased incidence of both nodule and thyroid cancer in patients with GD [23,24]. Chen et al. stated in their study that the risk of malignancy increased 1.3 times in GD. Stocker et al. stated that cancer rates in patients with GD vary between 1-9%. Despite the existence of the contradicting publications in the literature [25], we believe the nodules should be evaluated and managed according to published guidelines [22] regarding thyroid nodules in euthyroid individuals. So, we perform an algorithm for evaluation and management of patients with thyroid nodules based on sonographic pattern in patients with nodular GD as in euthyroid individuals. In our study, 33 patients had benign FNAB results in the elective group, while in the emergency group only 1 patient had a nodule with a benign cytology. On the other hand, 8 patients in the elective group had suspicious (>Bethesda 3) findings

TABLE II- *Perioperative outcomes of patients*

Parameter	Elective Group (N=101)	Urgent Group (N=12)	P Value
Treatment in emergency admission, n (%)			
Lugole	-	6 (50)	
Plasmapheresis	-	3 (25)	N/A
Steroid	-	2 (16.7)	
Steroid + Lugole	-	1 (8.3)	
Pre-operative Lab values (Mean±SD)			
‡FT3 (pg/mL)	3.4±0.7	4.7±2.6	<0.001
‡FT4 (ng/dL)	0.9±0.6	1.7±1.2	0.001
§TSH (IU/mL)	1.7±0.2	0.2±0.09	0.052
Post-operative complications, n (%)			
Requirement of Surgery due to bleeding	4 (3.9)	-	0.338
Transient Hypocalcemia	37 (36.6)	4 (33.3)	0.821
Transient *RLN palsy	8 (7.9)	2 (16.6)	0.356
Permanent Hypocalcemia	2 (1.9)	-	0.501
Permanent RLN palsy	1 (0.9)	-	0.634
Post-operative Calcium, mg/dL (Mean±SD)	8.0±0.1	8.2±0.3	0.669
Final Histopathology, n (%)			
Benign	92 (91.1)	12 (100)	0.146
Malign	9 (8.9)	-	
Histopathologic results in details, n (%)			
Benign	92 (91.1)	12 (100)	
Papillary Thyroid Carcinoma (Classical variant)**	1 (0.9)	-	0.348
Papillary Thyroid Carcinoma (Folliculary variant)†	1 (0.9)	-	
Micropapillary Thyroid Carcinomaø	7 (6.9)	-	
FNAB & Final Histopathology Relevance, n			
Yes**	1	1	
Missed¶	2	-	N/A
No FNAB	6	-	

‡FT3/4: Free T3/4, §TSH: Thyroid-Stimulating Hormone, *RLN: Recurrent Laryngeal Nerve,
** FNAB (Fine Needle Aspiration Biopsy) was Bethesda 4, † FNAB was Bethesda 2, ø Micropapillary carcinoma as incidental finding,
¶ One of the biopsied nodules had 1 mm tumor foci was revealed in final histopathology and one other nodule was evaluated as Bethesda 2 in FNAB but follicular variant papillary thyroid carcinoma was revealed in final histopathology.
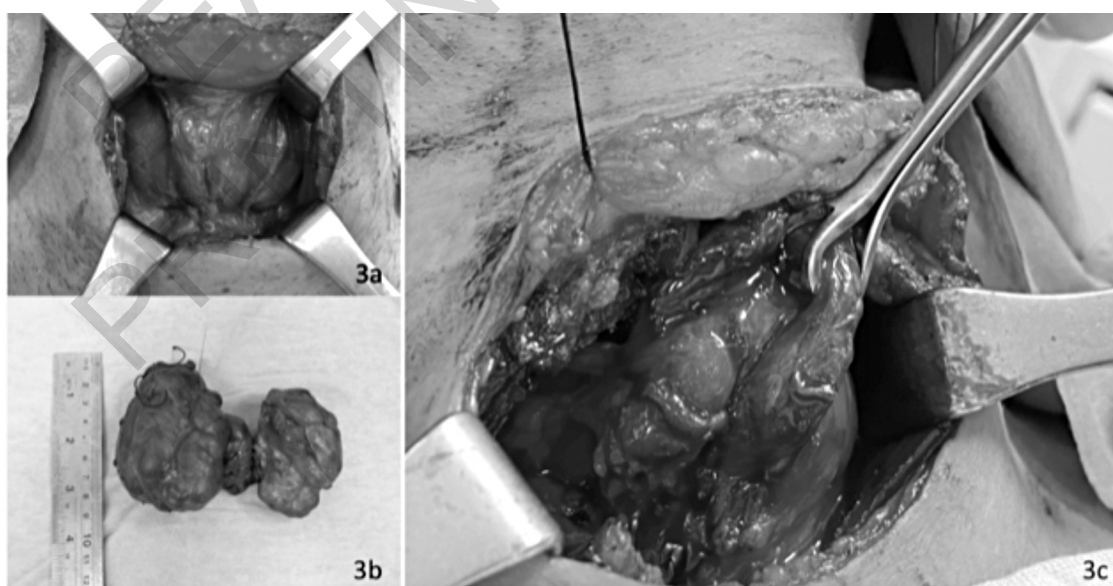

Fig. 3: Peroperative findings of Graves' disease. (3a) The photo shows diffuse hyperplasia of thyroid gland, (3b) Hyper vascular thyroid gland, (3c) Total thyroidectomy specimen.
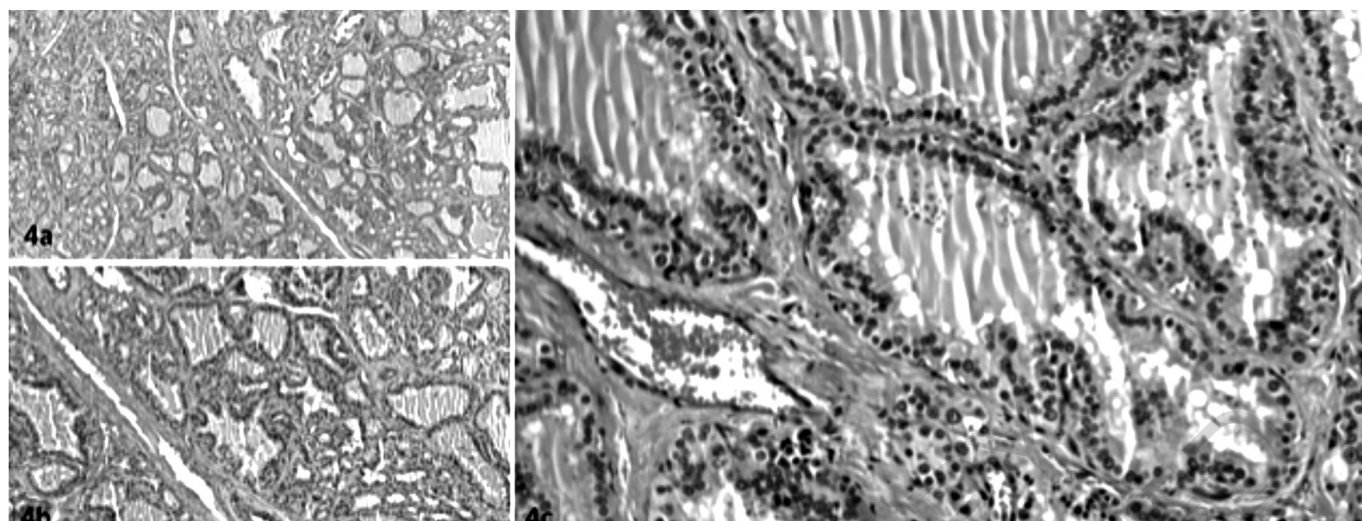
Fig. 4: Microscopic pathology slide of Graves' thyroid tissue. (4a) The picture shows diffuse hyperplastic thyroid tissue separated by fibrous bands (H&Ex100), (4b) Irregular folded follicles are seen in nodular areas (H&Ex200), (4c) At high magnification, it is observed that colloids show secretory changes due to hyper function (H&Ex400).

(p=0.003) in the FNAB. Micro focal tumor focus was detected in 1 of the 33 patients evaluated as benign by FNAB. In addition, classical variant papillary thyroid carcinoma was detected in a patient whose FNAB result was Bethesda 4. Thus, FNA and final histopathology were incompatible in 2 patients (Table II).

ATDs can be used as primary treatment (given for 6-18 months) (2). The thionamide antithyroid drugs MMZ and PTU inhibit thyroid hormone synthesis by interfering with thyroid peroxidase (TPO) [26,27].

Agranulocytosis, vasculitis, and hepatotoxicity were more common with PTU, according to ATA 2016 hyperthyroidism guidelines [28]. Because of this, the Food and Drug Administration (FDA) issued a safety alert in 2010 regarding the use of PTU due to the of risk fulminant hepatic necrosis. So MMZ is recommended in virtually every patient who chooses antithyroid drug therapy for GD, except during the first trimester of pregnancy when PTU is preferred.

Therefore, the rate of using methimazole was higher in our study (n=71, p<0.0001). However, the prescription of PTU continues widely among some clinicians. We have noticed that the majority (75%) of the patients who underwent urgent surgery were under PTU treatment (p=0.0001). In the majority of the patients in the urgently operated group, treatment was initiated by clinicians practicing outside of our clinic and hospital and those patients were consulted to us because of the side effects of their medications. An urgent need for surgery originated in these patients who discontinued their medication due to side effects. So, higher PTU use in the urgent group could be expected due to these major side effects risk of PTU.

The average length of hospital stay was 8 days for rapid optimization in the endocrinology department.

Recent American Thyroid Association (ATA) Guidelines recommend that if surgery is the treatment of choice for GD, then the patient should be in an euthyroid state [9]. Rendering patients euthyroid can be achieved by varying combinations of ATD and other drugs (Lugol's solution, dexamethasone, ß-blocker and cholestyramine). In this study, preoperative FT4 and FT3 levels were significantly higher (p<0.001 and p=0.001, respectively) than well controlled group similar to the recent study by Ali et al. in 2019 (29). Moreover; in 2005, Wen-Tsai et al. revealed that serum FT4 and FT3 levels were significantly lower with Graves' combination therapy (ATD, cholestyramine, ß-blocker) compared to ATD and ß-blocker therapy [30].

Treatment with ATDs is sufficient to achieve euthyroidism prior to surgery. ATDs are generally well tolerated, but rarely, major side effects may be observed. Major adverse effects of ATD therapy are agranulocytosis, vasculitis and hepatotoxicity [9]. In our study, major adverse effects were observed in 12 patients who underwent urgent surgery. When it is not possible to attain an euthyroid state with ATD because of the major side effects, the patient should be treated with ß-blockers, Lugol's solution, glucocorticoids, cholestyramine and plasmapheresis prior to thyroidectomy [9]. We selected the treatment according to the severity of the patients. We preferred plasmapheresis in patients with moderate-serious clinical hyperthyroidism as in our 3 cases and Lugol's solution, glucocorticoids, cholestyramine were administered in patient with mild clinical hyperthyroidism as in our 9 cases. ß-blocker was given to all patients.

Total thyroidectomy in the setting of GD may be more technically challenging due to chronic inflammation and increased vascularity [12]. Therefore, the risk of hematoma is greater following thyroidectomy for GD. Potential complications such as RLN injury, hematoma and hypoparathyroidism are higher in surgery than other

benign thyroid diseases [5,31]. For sure, the most serious complication of total thyroidectomy is the injury to the RLN and airway obstruction necessitating tracheotomy. The prevalence of transient or permanent RLN paresis was no different between the two groups of patients (p=0.356, p=0.634, respectively). Rates of recurrent laryngeal nerve injury reported in the literature range between 1-4% in GD patients, who underwent total thyroidectomy [32-35]. In our study, the rate of permanent RLN was 0.9% in the elective group, and there was no RLN paralysis encountered in the urgent group.

An increased rate (2.8%) of bleeding has been reported in GD compared to other thyroid diseases requiring surgery [31]. Some other studies also have reported a higher risk of postoperative hematomas in patients with GD [36,37]. In our series, post-thyroidectomy bleeding occurred only in 4 patients in elective group, which is compatible with the recent literature [29] and we did not encounter any bleeding in urgent group (p=0.338).

Postoperative hypocalcemia has been suggested to result from several mechanisms including abnormal release of calcitonin by manipulation of the thyroid and thyrotoxic osteodystrophy (hungry bone syndrome) [38]. Transient hypocalcemia may occur at higher rates (6.9% to 46%) in hyperthyroid patients due to increased bone turnover [39-42]. Permanent hypocalcemia rates after total thyroidectomy for GD are reported to be between 3-4% [32,33]. As distinct from literature, Welch et al. revealed that GD patients had a transient hypocalcemia rate of 72% and a permanent hypocalcemia rate of 1% [39]. Whereas Edafe et al. showed that the incidence of transient and permanent hypocalcaemia was 27% and 1% respectively [43]. In our study, no difference was found between groups in terms of postoperative calcium levels (p=0.669). Forty-one patients (36.2%) had transient and 2 patients (1.9%) had permanent hypocalcemia. But there was no significant difference in transient or permanent hypocalcemia between two groups (p=0.821 and p=0.501, respectively).

The retrospective design is the major limitation of our single center study.

In conclusion, despite the retrospective design, this study demonstrates that urgent total thyroidectomy in poorly controlled GD is an effective treatment option and seems preferable in life-threatening circumstances. With an appropriate preoperative preparation in concordance with the endocrinology department, it is as effective and safe as elective surgery. With regard to the definitive assessment of the safety and tolerability of the applied treatment regimen further studies with larger patient numbers are needed.

Riassunto

Il trattamento chirurgico della malattia di Graves (GD) è caratterizzata da un aumento del rischio di sanguinamento, di conseguente ipotiroidismo e paralisi ricorrente del nervo laringeo (RLN) rispetto ad altre indicazioni di tiroidectomia benigna. Tuttavia, può essere fatto in sicurezza nei centri ad alto volume. In alcuni casi particolari (cioè intolleranza ai farmaci antitiroidei o tireotossicosi), potrebbe essere necessario un trattamento chirurgico urgente. In questo studio, abbiamo mirato a confrontare le complicanze della tiroidectomia nella gestione urgente ed elettiva della malattia di Graves.

Metodi: 113 pazienti sottoposti a tiroidectomia totale per morbo di Graves tra il 2012-2019 sono stati valutati retrospettivamente in termini di dati demografici, risultati di laboratorio preoperatori, gestione, ricoveri ospedalieri, breve termine operatorio e postoperatorio esiti, morbilità e mortalità. 12 pazienti ricoverati in un reparto di endocrinologia per ipertiroidismo incontrollabile e complicazioni correlate, e che erano stati preparati per un intervento chirurgico con soluzione di Lugol, plasmaferesi e steroidi, sono stati considerati come gruppo destinato a chirurgia in urgenza,. I restanti 101 pazienti sono stati sottoposti a chirurgia elettiva: Gruppo in Elezione.Sono stati confrontati gli esiti chirurgici a breve termine, i tassi di morbilità e mortalità.

Risultati: Dei 113 pazienti che sono stati operati per GD, 92 erano donne e 21 erano maschi. Nel gruppo operato con urgenza, i livelli di FT4 e FT3 erano significativamente più alti (p <0,001 ep = 0,001, rispettivamente). Non c'era alcuna differenza significativa nell'ipocalcemia transitoria o permanente (p = 0,821 ep = 0,501, rispettivamente), paralisi RLN transitoria o permanente (p = 0,356, p = 0,634, rispettivamente) e sanguinamento postoperatorio (p = 0,338), tra chirurgia elettiva e gruppi di ottimizzazione rapida.

Conclusione: La chirurgia d'urgenza per la malattia di Graves può essere eseguita in sicurezza con l'applicazione di protocolli di trattamento preoperatorio efficaci.

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