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ORIGINAL ARTICLE

Total Thyroidectomy in the Management of Graves' Disease

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Abstract

Background: **Graves' disease (GD) is an autoimmune disorder of the thyroid gland in which thyrotropin receptor antibodies stimulate thyroid stimulating hormone receptors, thereby increasing thyroid hormone production and release.**
Aim and objectives: **The aim of this work was to evaluate the outcome of total thyroidectomy (TT) in the treatment of GD.**
Patient and methods: **Fifty patients have goiter was prospectively studied. All patients were undergoing capsular dissection TT after preoperative preparation at Al-Hussein University Hospital.**
Result: **As regard Postoperative parameters distribution between the two studied groups, we found that there is a significant difference between the two studied groups regarding thyroid stimulating hormone, free T4, and free T3.**
Conclusion: **TT for GD is a challenging procedure with a high rate of major complications. To reduce the major complications rate, inexperienced thyroid surgeons should remain vigilant when performing TT for GD. It is also suggested that inexperienced surgeons should improve the technique to safely preserve the function of RLN and PGs in regular thyroid surgeries before performing operations on GD patients. Updates on surgical concepts and the effective use of operative adjuncts (i.e., EBD) are necessary to improve patient safety and functional outcomes.**

Keywords: Antithyroid medication, Graves 'disease, Hyperthyroidism, Total thyroidectomy

1. Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism affecting 0.5 percent of the population with a marked female preponderance—Primary surgical management is uncommon and referral usually follows the failure of medical therapy and radioiodine ablation or for specific indications including patient preference, pregnancy, and severe eye disease.[1]

GD can be treated by antithyroid medication, radioactive iodine and surgery. When surgical treatment is indicated or selected for patients with GD, bilateral subtotal thyroidectomy (STT) has been recommended as the standard surgical procedure. The goal of STT is to obtain rapid control of thyroid function by removing the pathological gland and leaving a small remnant of thyroid tissue to maintain adequate hormone production, while being a relatively safe operation with low complication rates. However, recurrent hyperthyroidism from the remnant thyroid tissues occurs during long-term follow-up.[2]

Surgery is effective in the management of patients with GD. It provides rapid control of hyperthyroidism and a high cure rate.[3] Two surgical options are available: subtotal thyroid resection aiming to preserve thyroid function and TT to ablate thyroid function eliminating the risk of recurrent toxicity and reoperation.[3]

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Before 1992, the policy in Aberdeen was to preserve thyroid function. Remnant judged sufficient to permit recovery of normal thyroid function (bilateral subtotal lobectomy or lobectomy and contralateral subtotal lobectomy [Dunhill procedure]). After 1992, TT was progressively adopted becoming the operation of choice in 1999 ‘Although TT has been associated with an increased risk of complications.[4] with increasing experience and better training, TT can be performed safely.[5]

The aim of this work was to evaluate the outcome of TT in the treatment of GD.

2. Patients and methods

This was a clinical trial in which fifty patients have goiter was prospectively studied. All patients were undergoing capsular dissection TT after preoperative preparation at Al-Hussein University Hospital.

Patients of both sexes and in different age groups was included

For each patient beside thorough history and usual routine preoperative investigations, thyroid profile, neck ultrasonography, chest and neck X-rays, thyroid scan when indicated, fine needle aspiration cytology (FNAC) when indicated and referral to ENT specialist for preoperative assessment of vocal cords.

Inclusion criteria: include patients presented with GD and patients with benign non-GD scheduled for TT, including Simple multinodular goiter, secondary toxic goiter, and selected cases of thyroiditis.

Exclusion criteria: include recurrent goiter, thyroid malignancy and completion thyroid surgery.

These patients were divided into two groups according to presence or not of GD:

Group 1 (Graves' group): include 25 patients and includes patients presented by primary toxic goiter with pregnancy, severe eye disease, failure of medical treatment, patient preference of surgical intervention, and other patients with Graves' accepts to shares in this study.

Group II (NonGraves' group): include 25 patients and includes patients presented with benign non-GD scheduled for TT, including Simple multinodular goiter, secondary toxic goiter, and selected cases of thyroiditis.

GD and secondary toxic goiter were prepared before surgery by using Carbimazole, Propranolol, and Lugol's Iodine.

Written informed consent was taken and all patients were informed that they have to take postoperative hormonal replacement for long life.

Operative notes were recorded, including operative procedure, intraoperative complications, operative time, intraoperative blood loss and inspection of vocal cords during recovery from anesthesia.

All the removed thyroid specimens were sending for histopathological examinations.

All patients was followed up postoperatively by clinical evaluation, thyroid profile, and by serum calcium, phosphorus, and albumin in some patients for 6 months after discharge from the patients complaining of voice abnormalities, dyspnea, or stridor, indirect laryngoscopy were done at 1, 3 and 6 months after surgery for assessment of vocal cords. Both hypocalcaemia and laryngeal nerve injury was considered permanent if they had not resolved 6 months after surgery.

A comparison was made between the two groups as regard; operative time, amount of intraoperative blood loss, postoperative bleeding or amount of postoperative suction drain drainage, seroma formation, wound sepsis, postoperative pain, RLN injury, postoperative hypocalcaemia, and length of hospital stay.

2.1. Statistical analysis

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact were used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation) for parametric and median and range for non-parametric data. Independent T-test and Mann–Whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables respectively. All statistical comparisons were two tailed with significance Level of P value ≤ 0.05 indicates significant, $P < 0.001$ indicates highly significant difference, while $P > 0.05$ indicates nonsignificant difference.

3. Discussion

The use of TT remains controversial for small differentiated thyroid carcinomas, but even more controversial is its use to treat benign diseases. Most surgeons avoid the procedure owing to the possible complications such as permanent recurrent laryngeal nerve palsy and permanent hypoparathyroidism; STT has been the preferred operation for benign thyroid diseases.[6]

The purpose of this study was to evaluate the outcome of TT in the treatment of GD.

This was a comparative study; Fifty patients have goiter were prospectively studied. All patients were undergone capsular dissection TT after preoperative preparation at Al-Hussein University Hospital. Patients were divided into two groups; Group 1 (Graves' group): include 25 patients and includes patients presented by primary toxic goiter with pregnancy, severe eye disease, failure of medical treatment, patient preference of surgical intervention, and other patients with Graves' accepts to shares in this study. Group II (Non-Graves' group), include 25 patients and includes patients presented with benign non-GD scheduled for TT, including Simple multinodular goiter, secondary toxic goiter and selected cases of thyroiditis.

Analysis of our findings revealed that Mean ± SD of age was 45.79 ± 9.42 and 44.37 ± 7.35 in group A and B respectively, There is no significant difference between the two studied groups regarding age, sex, BMI, SBP, DBP and smoking.

In line with our findings, **Cipolla** et al.,[7] reported that a total of 594 patients underwent TT for GD at the Department of Surgical, Oncological and Oral Sciences (University of Palermo) from 2008 to 2018. The mean age of the patients was 44.7 ± 12.7 years: 138 (23.2%) patients were males and 456 (76.7%) were females. The majority of patients were euthyroid or mildly hyperthyroid at the time of thyroidectomy. A history of GO was present in 196 patients (32,9%) and, in most cases, in progression.

Yanaia et al.,[8] reported that among 91 patients who showed hyperthyroidism, they found 74 patients with GD including thyroid storm ($n = 5$), and seven with painless thyroiditis and 10 with subacute thyroiditis. There were no significant differences in age, body temperature, and pulse rate among such diseases. GD patients included a significantly higher percentage of female patients than painless thyroiditis and sub-acute thyroiditis patients.

In the current study, it was noted that there is no significant difference between the two studied groups regarding CBC, liver enzymes, and kidney function tests.

In comparison with our findings, **Yanaia** et al.,[8] reported that WBC count was significantly higher in sub-acute thyroiditis than in GD. The percentage of neutrophil among WBC was significantly higher in sub-acute thyroiditis patients than in GD patients. Furthermore, the percentages of lymphocyte and eosinophil in sub-acute thyroiditis were significantly lower than those in GD Serum albumin level was significantly lower in subacute thyroiditis than in GD. Serum levels of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were significantly higher in GD than in painless thyroiditis. Serum creatinine level was significantly lower in GD than in painless thyroiditis. Serum CRP level was significantly higher in subacute thyroiditis than in GD.

In the current study, we found that there is no significant difference between the two studied groups as regard electrolytes.

Bharti et al.,[9] found in their study that there was a significant decrease in calcium in hypothyroidism and subclinical hypothyroidism patients. This is mainly due to the effect of decreased levels of thyroxin. Thyroxin normally regulates calcium by releasing calcium ions from the cells. In addition, they reported significantly high phosphorus levels in hypothyroidism and subclinical hypothyroidism as well.

Sun et al.,[10] also reported that hyponatremia was not a common finding among their population with extreme TSH elevations. This was also supported by **Wolf** et al.,[11] who reported that the co-occurrence of hyponatremia with hypothyroidism is probably a coincidence and attributable to other causes.

In the current study, there is a significant difference between the patients with Graves' and without GD regarding TSH and free T4.

Yanaia et al.,[8] reported that there was no significant difference in TSH level among such diseases. Serum FT3 level in GD patients was significantly higher than that in painless thyroiditis and subacute thyroiditis patients. Serum FT4 level and the ratio of FT3 to FT4 were significantly higher in GD than in painless thyroiditis. The third-generation thyrotropin receptor antibodies and anti-thyroid peroxidase antibody (TPO-Ab) levels were significantly higher in GD than in the other two diseases. Antithyroglobulin antibody (Tg-Ab) level in GD was significantly higher than that in subacute thyroiditis.

Furthermore, **Sultan** et al.,[12] reported that T3 and T4 levels in blood were determined in all patients and revealed that 28 patients (70%) were euthyroid (normal T3, T4), two patients (5%) were hypothyroid, and the remaining 10 patients (25%) were hyperthyroid (toxic). Gland nodularity was found in 36 patients (90%), tracheal shift in two patients (5%), and retrosternal extension in two patients (5%).

TT has an important role in the management of patients with benign diseases when both lobes of the thyroid gland are involved. This approach avoids recurrence and increased risk of morbidity associated with secondary operation.[13]

The rate of complications associated with TT, namely recurrent nerve palsy, hypocalcemia, wound infection, and secondary hemorrhage, did not differ significantly from that associated with STT. These findings indicate that TT is an acceptable surgical alternative in benign multinodular goiters.[14]

As regard Postoperative parameters distribution between the two studied groups, we found that there is a significant difference between the two studied groups regarding TSH, free T4, and free T3.

In the harmony with our findings, **Senese** et al.,[15] which aimed to assess the impact of TT on thyroid function. Surgery had a significant impact on TSH, T4, T3, and thyroglobulin levels. Significant differences between the mean levels at the three times of surgery (T_0, T_1, and T_2) were observed ($P < 0.001$). Surgery produced a significant increase in T4 and thyroglobulin levels intraoperatively. Furthermore, surgery led to a significant decrease in TSH, T4, T3, and thyroglobulin levels postoperatively.

On the other hand, as regard Operative time and hospital stays between the two studied groups, we found that there is no significant difference between the two studied groups regarding operative time and hospital stay.

While, **Cipolla** et al.,[7] reported that the surgical drainage was always removed within 24 h after surgery. The majority of patients (428 patients, 72.1%) were discharged within 48 h after thyroidectomy; the duration of hospitalization for the remaining cases was between 4 and 9 days. In only 3 cases (0.5%) an emergency reoperation was required due to a postoperative hematoma.

Moreover, **Dedivitis** et al.,[16] reported that the mean duration of hospital stay for patients undergoing thyroidectomy was 1.02 days. The 265 patients (98.5%) were discharged in the morning of postoperative day 1. As far as concerns the 4 patients who required readmission due to hypocalcaemia, the overall duration of hospitalization was 1.05 days.

Similar to the reported literature, **Lui** et al.,[17] reported that patients who underwent TT had significantly more hypocalcemia with no difference in rates of recurrent laryngeal nerve injury. Despite this, both patient groups had comparable length of stay postsurgery. This seems to suggest that even though patients were more likely to experience hypocalcemia post-TT, the severity of hypocalcemia was not significantly more severe than those who underwent ST, as this would have necessitated intravenous calcium replacement which would have translated into longer hospitalization stay postoperatively.

In the present study, postoperative complications were higher among graves group compared to nongraves group but without statistically significant difference.

In a meta-analysis regarding 35 studies, comprising 7241 patients, **Palit and Miller**,[18] observed a 7.9% rate of recurrent or persistent hyperthyroidism in patients who had undergone ST, whereas a 0% rate was observed in those who had undergone total and/or near-TT. Moreover, the permanent RLN palsy rate was 0.9% after TT and 0.7% after ST. Remarkably, permanent hypoparathyroidism occurred in 0.9% of patients after TT and in 1% of patients after ST.

In a recent article analyzing the long-term outcomes of thyroid function after STT for GD, **Lin** et al.,[19] observed a persistent or recurrent hyperthyroidism in 28.7% of patients and hypothyroidism in over 50% of patients.

TT is a safe and effective therapy for GD. In the series of **Shinall** et al.,[20] , the most common complication, hypocalcemia, was, in general, transient. The most feared complication, RLN paresis, was uncommon and also generally transient. Rates of both complications (transient and permanent) were comparable with those demonstrated in previous studies of total and STT for GD and after TT for nontoxic multinodular goiter. In these studies, the incidence of transient hypocalcemia ranged from 3 to 40%, with the incidence of long-term hypocalcemia ranging from 0.6 to 6%. Similarly, the incidence of transient and permanent RLN palsy ranged from 0 to 24%, and 0–2%, respectively[21,22]

In the series of **Shinall** et al.,[20] other complications, such as hematoma, seroma, and tracheal injury, occurred at very low rates. These data reconfirm the consensus that TT is a safe and appropriate initial therapy for GD when performed by high-volume surgeons.

Current ATA guidelines recommend that patients be rendered euthyroid with methimazole preoperatively and that KI be given in the immediate preoperative period. The recommendation to render patients euthyroid with antithyroid medication stems from a concern that the stress of surgery could precipitate thyroid storm. In **Shinall** et al.,[20] series, the majority of patients were treated with anti-thyroid medications and no patient suffered from thyroid storm, even though a large proportion (42%) remained biochemically hyperthyroid at the time of operation. While the moderately and severely hyperthyroid patients did require more intraoperative beta-blockers, there was no evidence for any other untoward cardiovascular outcomes resulting from hyperthyroidism. On bivariate analysis, association between hyperthyroidism and complications approached statistical significance, but did not reach it ($P = 0.059$). Adjusting for other factors via multivariate analysis, the association between hyperthyroidism and complications still failed to reach statistical significance ($P = 0.120$). Thus, while we believe preoperative medical management is absolutely justified on the basis of symptom management, these data suggest that patients who remain biochemically hyperthyroid before surgery can still have good surgical outcomes.

4. Conclusion

In conclusion, TT for GD is a challenging procedure with a high rate of major complications. To reduce the major complications rate, inexperienced thyroid surgeons should remain vigilant when performing TT for GD. It is also suggested that inexperienced surgeons should improve the technique to safely preserve the function of RLN and PGs in regular thyroid surgeries before performing operations on GD patients. Updates on surgical concepts and the effective use of operative adjuncts (i.e., EBD) are necessary to improve patient safety and functional outcomes Tables 1–7.

Table 1. Demographic data of the two studied groups.

RESULTS				
Variable	Graves ($n = 25$)	No Graves ($n = 25$)	t/χ^2	*P*
Age (years) Mean ± SD	45.79 ± 9.42	44.37 ± 7.35	0.594	0.555
Sex				
Female	16 (64%)	14 (56%)	0.333	0.564
Male	9 (36%)	11 (44%)		
BMI (kg/m^2) Mean ± SD	27.12 ± 3.57	26.53 ± 2.96	0.636	0.528
SBP (mmHg) Mean ± SD	125.78 ± 4.81	123.67 ± 2.74	1.91	0.063
DBP (mmHg) Mean ± SD	80.89 ± 13.84	79.78 ± 3.53	0.389	0.699
Smoking	10 (40%)	8 (32%)	0.347	0.556

There is no significant difference between the two studied groups regarding age, sex, BMI, SBP, DBP, and smoking.

Table 2. Preoperative Laboratory parameters between the two studied groups.

	Graves ($n = 25$)	No Graves ($n = 25$)	t	*p*
Hemoglobin (g/dl) Mean ± SD	11.55 ± 1.64	12.18 ± 1.43	1.45	0.154
TLC (10^3/μL) Mean ± SD	8.12 ± 2.32	6.87 ± 3.02	1.64	0.107
PLT (10^3/μL) Mean ± SD	273.44 ± 35.92	268.18 ± 37.87	0.504	0.617
RBS (mg/dl) Mean ± SD	116.14 ± 19.61	125.57 ± 16.84	1.82	0.074
Serum Creatinine (mg/dl) Mean ± SD	0.654 ± 0.154	0.712 ± 0.163	1.29	0.202
BUN (mg/dl) Mean ± SD	19.25 ± 5.27	17.32 ± 5.64	1.25	0.217
AST (U/L) Mean ± SD	31.65 ± 8.56	33.38 ± 10.6	0.635	0.529
ALT (U/L) Mean ± SD	30.09 ± 10.01	28.36 ± 9.11	0.639	0.526

This table shows that there is no significant difference between the two studied groups regarding laboratory parameters.

Table 3. Preoperative electrolytes distribution between the two studied groups.

	Graves ($n = 25$)	No Graves ($n = 25$)	t	*p*
Sodium (mEq/L) Mean ± SD	136.61 ± 5.27	138.74 ± 3.56	1.67	0.101
Potassium (mEq/L) Mean ± SD	4.72 ± 0.643	4.78 ± 0.684	0.320	0.751
Calcium (mg/dl) Mean ± SD	8.86 ± 1.34	9.13 ± 1.2	0.751	0.457
Phosphate (mg/dl) Mean ± SD	5.24 ± 1.08	5.19 ± 0.954	0.173	0.863
Magnesium (mg/dl) Mean ± SD	2.52 ± 0.716	2.29 ± 0.403	1.4	0.168

This table shows that there is no significant difference between the two studied groups.

Table 4. Preoperative Thyroid function distribution between the two studied groups.

	Graves ($n = 25$)	No Graves ($n = 25$)	t	*p*
TSH (mU/L) Mean ± SD	7.43 ± 2.81	4.85 ± 1.14	**4.25**	**<0.001**
Free T_4 (pmol/L) Mean ± SD	11.25 ± 1.79	15.36 ± 1.24	**9.44**	**<0.001**
Free T_3 (pmol/L) Mean ± SD	4.37 ± 1.01	4.79 ± 1.13	1.39	0.172

This table shows that there is a significant difference between the two studied groups regarding TSH and free T4.

Table 5. Postoperative parameters distribution between the two studied groups.

	Graves ($n = 25$)	No Graves ($n = 25$)	t	p
Sodium (mEq/L) Mean ± SD	135.29 ± 5.46	136.18 ± 3.89	0.664	0.510
Potassium (mEq/L) Mean ± SD	5.13 ± 0.844	4.95 ± 0.817	0.766	0.447
Calcium (mg/dl) Mean ± SD	7.73 ± 1.56	8.18 ± 1.39	1.08	0.287
Phosphate (mg/dl) Mean ± SD	5.62 ± 1.23	5.83 ± 1.14	0.626	0.534
TSH (mU/L) Mean ± SD	3.52 ± 0.981	1.74 ± 0.532	8	**<0.001**
Free T_4 (pmol/L) Mean ± SD	10.16 ± 1.22	14.1 ± 1.31	10	**<0.001**
Free T_3 (pmol/L) Mean ± SD	2.35 ± 0.812	2.98 ± 0.877	**2.64**	**0.011**

This table shows that there is a significant difference between the two studied groups regarding TSH, free T4, and free T3.

Table 6. Operative time and hospital stays between the two studied groups.

	Graves ($n = 25$)	No Graves ($n = 25$)	t	p
Operative time (min) Mean ± SD	113.54 ± 52.47	102.74 ± 49.56	0.748	0.458
Hospital stay (days) Mean ± SD	3.26 ± 0.749	2.79 ± 0.916	1.98	0.053

This table shows that there is no significant difference between the two studied groups regarding operative time and hospital stay.

Table 7. Postoperative complications between the two studied groups.

	Graves ($n = 25$)	No Graves ($n = 25$)	χ^2	p
Temporary hypoparathyroidism	7 (28%)	2 (8%)	3.39	0.066
Permanent hypoparathyroidism	1 (4%)	0	1.02	0.315
Temporary RLN palsy	3 (12%)	1 (4%)	1.09	0.299
Permanent RLN palsy	1 (4%)	0	1.02	0.315
Postoperative bleeding	2 (8%)	0	2.08	0.149
Wound infection	2 (8%)	1 (4%)	0.355	0.552
Seroma	1 (4%)	1 (4%)	–	1

This table shows that postoperative complications were higher among graves group compared to nongraves group but without statistically significant difference.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

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Conflict of Interest

The authors declared that there were no conflicts of interest.

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