Permanent hypocalcemia in patients operated for thyroid carcinoma

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Abstract

Aim and objective The incidence and risk factors for permanent hypocalcemia in thyroid carcinoma were investigated.

Materials and methods The records of 417 patients were reviewed retrospectively at tertiary oncology referral center. Total or subtotal thyroidectomy patients constituted group I (n = 225), reoperative thyroid surgery patients constituted group II (n = 106), and therapeutic neck dissection cases constituted group III (n = 86). Age, gender, thyroid functions, pathologically verified tumor type, differentiation, localization and size, multicentricity, thyroid capsule invasion, extrathyroidal soft tissue invasion, coexistence of lymphocytic thyroiditis, metastatic lymph nodes dissected, incidental parathyroidectomy, and the type of surgery were investigated.

Results Permanent hypocalcemia was seen in 32 (7.7%) patients. The incidence of permanent hypocalcemia for each group was 1.7%, 10.3% and 19.7%, respectively. Related risk factors were hyperthyroidism for group I [adjusted relative risk (RR) = 21.1, 95% confidence interval (CI) = 2.6–165, $p = 0.01$] incidental parathyroidectomy for group II (RR = 7.8, 95% CI = 1.9–31.0, $p = 0.004$), and extrathyroidal soft tissue invasion (RR = 3.1, 95% CI = 1.1–9.5, $p = 0.03$) for group III.

Conclusion Permanent hypocalcemia rate was increased with reoperative thyroid surgery and neck dissection added to total thyroidectomy. Hyperthyroidism, incidental parathyroidectomy and extrathyroidal extension were related risk factors.

Keywords Thyroid carcinoma · Hypocalcemia · Thyroidectomy

Introduction

Thyroidectomy is indicated in the treatment of all patients with differentiated thyroid carcinoma. Undifferentiated carcinomas are usually not resectable. Therapeutic neck dissection is performed in patients who either present with clinically evident lymphadenopathy or in whom imaging studies showed nodal metastasis with usually elevated blood thyroglobulin levels [1]. An exception to this is medullary thyroid carcinoma for which total thyroidectomy with prophylactic or therapeutic neck dissection is recommended.

The rates of expected complications increase with the diagnosis of malignancy. The major postoperative complications are vocal cord palsy, due to the dysfunction of the recurrent laryngeal nerves, and permanent hypocalcemia. Postoperative death is rare or even unrecorded [2].

The combined evaluation of benign and malignant thyroid diseases and different types of surgeries in the same study makes the description of related risk factors difficult. Therefore, in this study the incidence of permanent hypocalcemia in relation to the types of surgeries and other related factors was analyzed for patients with thyroid malignancy.

Materials and methods

Ethical consideration

The data was collected retrospectively and approved by our institutional ethical committee.

Study population

We reviewed the records of 417 patients who were diagnosed as thyroid carcinoma and treated in the Ankara Oncology

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Education and Research Hospital and postoperative permanent hypocalcemia together with related factors is investigated. Three hundred and sixteen patients (75.8%) were woman, 101 (24.2%) patients were man, and the median age was 41 (range, 11–89 years).

Definition for surgery and groups

Total thyroidectomy was described as the removal of all thyroid tissue in the first operation. Subtotal thyroidectomy was carried out by the capsular dissection method, and the whole involved lobe, the isthmus and medial third of the contralateral lobe was included in the resection. Reoperative thyroid surgery was used for the patients with remnant tissue defined by postoperative scan and with insufficiently elevated thyroid stimulating hormone (TSH) levels for radioiodine ablation treatment or for the patients with recurrence of the disease. Therapeutic neck dissection was performed to the patients either with lymph node involvement verified histologically or with imaging studies indicating nodal metastasis usually with elevated blood thyroglobulin levels. Prophylactic central compartment dissection has not been added to total thyroidectomy even for the patients with preoperatively documented thyroid carcinoma. Therefore, none of the patients except group III has been treated with central neck dissection. Total or subtotal thyroidectomy patients ($n=225$) constituted group I, reoperative thyroid surgery performed patients ($n=106$) constituted group II, and therapeutic neck dissection ($n=86$) patients constituted group III. Eighty patients in group III were also operated with simultaneous thyroid surgery. Fine needle aspiration or excisional biopsy of palpable lymph nodes was used for the histopathologic diagnosis of metastasis in 81 patients with lymph node dissection. Five more patients with suspected lymph node metastasis using imaging studies were evaluated with frozen section. Lymph nodes were defined following the nomenclature proposed by the Memorial Sloan-Kettering Cancer Center. Level I represent submental and submandibular groups, level II, III and IV represent upper, mid, and lower jugular groups, respectively, and level V posterior triangle nodes [3]. The patients were divided into two groups according to the type of neck dissection applied. Patients with dissection of lymph nodes at levels II, III and IV constituted selective lateral neck dissection, and those at levels I, II, III, IV and V constituted radical or modified radical neck dissection.

Preoperative evaluation

Complete medical history and physical examination, thyroid function test, fine needle aspiration or excisional biopsy, radiography of the thorax, and thyroid ultrasonography were used for preoperative evaluation. In all patients, indirect

laryngoscopic examination was used to evaluate vocal cord motility both before and after surgery. Preoperative calcium levels were strictly evaluated for every patient before grouping. Regardless of the type of surgery, parathyroid glands and recurrent laryngeal nerves were routinely identified and preserved before the ligation of the inferior thyroid vessels.

Definition of permanent hypocalcemia

Postoperative blood calcium levels were determined for all patients and the patients with hypocalcemia findings were followed-up with regular intervals. Hypocalcemia was considered whenever there was a need for exogenous calcium replacement to maintain normal levels in serum (8–10.4 mg/dl) or for eliminating the clinical signs and symptoms of the hypocalcemia. Hypocalcemia was considered permanent when calcium and vitamin D replacement was needed for more than 6 months to eliminate the signs and symptoms of hypocalcemia.

Related variables

Age, gender, thyroid functions, pathologically verified tumor type, differentiation, localization and size, multicentricity, thyroid capsule invasion, extrathyroidal soft tissue invasion, coexistence of lymphocytic thyroiditis, metastatic lymph nodes dissected, incidental parathyroidectomy, and the type of the surgery were the variables analyzed.

Statistical methods

Statistical analysis was performed using SPSS 13.0 software (Statistical Software, Chicago, USA). Univariate analysis of continuous variables was performed using a t-test, and categorical values were determined using the Chi-square test, or Fisher's exact test. Significance was determined for $p \leq 0.05$.

Results

Permanent hypocalcemia was seen in 32 (7.7%) patients. Distribution of patients in relation to histological type was; 329 patients had papillary carcinoma, 44 follicular carcinoma, 21 hurthle cell carcinoma, 15 anaplastic carcinoma, and 8 medullary carcinoma.

The type of the surgery

Permanent hypocalcemia developed in 4 (1.7%) out of 225 patients with total or subtotal thyroidectomy, 11 (10.3%)

out of 106 patients with reoperative thyroid surgery and 17 (19.7%) out of 86 patients with neck dissection. Simultaneous total thyroidectomy was also applied for all the patients that had been operated with lymph node dissection and developed permanent hypocalcemia. When different operations in group I were compared; permanent hypocalcemia was seen in 3 (1.5%) out of 192 patients with subtotal thyroidectomy and 1 (3%) out of 33 patients with total thyroidectomy. The incidence was similar for total thyroidectomy and subtotal thyroidectomy patients ($p = 0.47$). Permanent hypocalcemia rates were found to be higher for patients with reoperative thyroid surgery in comparison with the patients in group I. The risk was increased 6.3 times (95% CI 1.9–20.5) and this increase was significant ($p = 0.001$). The permanent hypocalcemia rate of thyroidectomy with lymph node dissection patients was significantly higher than thyroidectomy without lymph node dissection patients (21.2% vs 1.7%, respectively, $p = 0.001$). The risk was 14.9 times (95% CI 4.8–45.9) increased for thyroidectomy with lymph node dissection group. The types of neck dissection applied and the patients with permanent hypocalcemia were given in Table 1.

The other factors investigated for permanent hypocalcemia

The factors related and not related to permanent hypocalcemia are given in Tables 2 and 3. Incidental parathyroidectomy was present at histopathological examination of 25 (5.9%) patients out of 417 patients. Parathyroid glands were single for 19 patients and double for 6 patients. Incidental parathyroidectomy was documented for 3 patients (1.3%) operated with total thyroidectomy in group I, for 14 patients (13.2%) in group II and for 8 patients (9.3%) in group III. All these patients in group III had been operated with thyroidectomy and central neck dissection.

Univariate analysis

Related risk factors were hyperthyroidism for group I (RR = 21.1, 95% CI = 2.6–165, $p = 0.01$), incidental

parathyroidectomy for group II (RR = 7.8, 95% CI = 1.9–31.0, $p = 0.004$), and extrathyroidal soft tissue invasion (RR = 3.1, 95% CI = 1.1–9.5, $p = 0.03$) for group III. Reoperative thyroid surgery and the addition of neck dissection to thyroid surgery were significant factors for increased incidence ($p = 0.001$ and $p = 0.001$, respectively).

Discussion

Postoperative hypocalcemia is the most common and well-recognized immediate complication of thyroid surgery. Several thyroid conditions such as Graves' disease, recurrent thyroid disease, and thyroid carcinoma carry a higher risk of postoperatively developing transient and permanent hypocalcemia [4]. The reported complication rate for permanent hypocalcemia varies significantly, ranging from 0.5 to 11.0% [5]. Different types of surgeries and benign and malignant thyroid diseases in the same series make the description of related risk factors difficult. Therefore in this series, only the patients with thyroid malignancy were evaluated and put in groups according to the type of the surgeries.

In some other studies that compared total thyroidectomy with subtotal thyroid surgeries, permanent hypocalcemia rates were found to be higher in the former group and the conclusion was a correlation between the extent of surgery and the permanent hypocalcemia rates [6–9]. In a study by Thomusch et al. more extensive surgery increased the relative risk of permanent hypocalcemia by 1.5–1.8 times [6]. However, in some other studies, it was concluded that more radical surgery did not result in higher rates of hypoparathyroidism [10, 11]. In our study, when subtotal thyroidectomy was compared with total thyroidectomy, the extent of the surgery did not increase the permanent hypocalcemia rates.

In many reports by experienced surgeons, thyroid cancer operations and secondary surgeries were still associated with higher complication rates [12]. In our study, permanent hypocalcemia rates were higher in patients with reoperative thyroid surgery in comparison with group I, and this increase was significant. Similarly, in many other studies,

Table 1 The distribution of the patients according to the types of neck dissection

The type of dissection	Total patients (n)	PH (n)
Central dissection + TT	6	–
Central dissection + selective lateral ND + TT	28	6
Central dissection + modified radical ND + TT	41	10
Central dissection + bilateral modified radical ND + TT	5	1
Only selective lateral ND	1	–
Only modified radical ND	5	–

ND: Neck dissection; TT: Total thyroidectomy; PH: Permanent hypocalcemia.

Table 2 The categorical variables related to permanent hypocalcemia

		The number of patients with permanent hypocalcemia (PH)					
		Group I PH(+)/total	p	Group II PH(+)/total	p	Group III PH(+)/total	p
Gender	Man	1/50	1	1/16	0.88	4/36	0.15
	Woman	3/175		10/90		13/50	
Hyperthyroidism	No	2/213	0.01	11/102	1	16/84	1
	Yes	2/12		0/4		1/2	
Histological type	Papillary	4/176	0.36	10/80	0.36	16/73	0.29
	Follicular	0/27		0/15		0/2	
	Hurthle	0/11		1/8		0/2	
	Anaplastic	0/8		0/1		1/6	
	Medullary	0/3		0/2		0/3	
Differentiation	Well	4/194	0.47	10/94	0.87	16/69	0.29
	Moderate	0/19		1/9		0/7	
	Undifferentiated	0/9		0/1		1/7	
Tumor localization	Right lob	3/78	0.18	5/37	0.98	3/25	0.26
	Left lob	1/61		0/28		5/21	
	Bilateral	0/36		3/17		8/26	
	Unknown	0/50		3/24		1/14	
Tumor size (UICC staging)	T _x	0/35	0.28	2/16	0.95	1/17	0.69
	T ₁₋₂	3/99		5/46		6/30	
	T ₃	1/60		3/34		3/15	
	T ₄	0/31		1/10		7/24	
Multicentricity	Solitary	4/127	0.21	6/64	0.37	7/39	0.28
	Multicentric	0/59		4/29		8/30	
	Unknown	0/39		1/13		2/17	
Thyroid capsule Invasion	No	4/115	0.28	5/54	1	7/37	0.44
	Yes	0/78		4/37		10/34	
	Unknown	0/32		2/15		0/15	
Extrathyroidal soft tissue invasion	No	4/192	0.06	10/99	0.84	8/59	0.03
	Yes	0/33		1/7		9/27	
Lymphocytic thyroiditis	No	3/204	0.82	10/95	1	17/81	1
	Yes	1/11		1/9		0/2	
	Unknown	0/10		0/2		0/3	
Incidental parathyroidectomy	No	4/214	1	6/91	0.004	15/75	0.66
	Yes	0/3		5/14		2/8	
	Unknown	0/8		0/1		0/3	

Table 3 The continuous variables related to permanent hypocalcemia

		The number of patients with PH					
		Group I PH(+)/total	p	Group II PH(+)/total	p	Group III PH(+)/total	p
Age (median)	PH(–)	41	0.50	37	0.09	37	0.51
	PH(+)	36		46		37	
Metastatic lymph nodes	PH(–)					5.2 ± 0.7	0.36
	PH(+)					7.3 ± 2.0	

PH: Permanent hypocalcemia

the complication rates had not been shown to be increased with reoperative thyroid surgery [6, 7, 13]. Also, permanent hypocalcemia rates were found to be increased in patients with neck dissection [13, 14]. In a study by Bergamaschi et al. the permanent hypocalcemia rate was as high as 17.3% for the group with neck dissection [15]. In this series, permanent hypocalcemia rate in neck dissection group was 19.7% and all the patients were thyroidectomy with neck dissection patients.

The incidence of incidental parathyroidectomy during thyroid surgery ranges from 8 to 19%. Reoperative thyroid surgery or re-operations are associated with an increased risk for unintentional parathyroidectomy, probably resulting from the formation of scar tissue and fibrosis that cause operative difficulty [16]. While the removal of a single parathyroid gland is not associated with postoperative hypocalcemia, the removal of at least two parathyroid glands increases the risk of permanent hypocalcemia [9]. In a study by Lin et al. of the 25 repeat operations for recurrent or persistent malignancy, 5 (20%) were found to have unintentional parathyroid removal compared with 15 (7.7%) of 195 primary thyroidectomy patients [16]. However, there was no association between incidental parathyroidectomy and permanent hypocalcemia and there are many other studies in literature to support this occurrence [8, 9]. In this series, the whole incidence of incidental parathyroidectomy was 5.9%. All patients with incidental parathyroidectomy in group I were total thyroidectomised. This rate was even higher for reoperative thyroid surgery (13.2%) and neck dissection groups (9.3%). Besides, this rate was correlated with permanent hypocalcemia rates in reoperative thyroid surgery performed group. In another series of 5,846 patients, incidental parathyroidectomy was shown to be a risk factor for permanent hypocalcemia [6].

We could not find any data reporting the association between the thyroid capsule or extrathyroidal soft tissue invasion with permanent hypocalcemia in the literature published in English. In this study, although the relation with thyroid capsule invasion could not be demonstrated, extrathyroidal soft tissue invasion was found to a risk factor for permanent hypocalcemia at univariate analysis. Soft tissue invasion was thought to be a marker of tumor aggressiveness and lymph node metastasis was also present in majority of this group of patients. Repeated surgery and neck dissection added to thyroid surgery are the procedures of choice for many of the patients in this group.

In a study of 1,192 thyroidectomies including 87 total thyroidectomies in conjunction with neck dissection, Bergamaschi et al. were unable to demonstrate any correlation between the number of resected lymph nodes and the overall degree of permanent hypocalcemia [15]. In our series of 417 thyroidectomies including 80 total thyroidectomies in conjunction with neck dissection. In our

series, the number of metastatic lymph nodes was not a risk factor for permanent hypocalcemia.

The National Hospital Data Survey database was examined by Bhattacharyya and Fried and in their retrospective study of 517 patients; younger age was statistically associated with an increased incidence of hypocalcemia [17]. In a study of 7,266 patients with benign thyroid disease by Thomusch et al., advanced age was found to be associated with permanent hypocalcemia [6]. In another study of 316 patients with differentiated thyroid carcinoma by Filho and Kowalski, age and gender were not associated with permanent hypocalcemia [13]. In a study by Prim et al., gender was found to be related to permanent hypocalcemia [7]. In our series of 282 patients, age and gender were not found to be related to permanent hypocalcemia.

In another study of 1,020 patients by Filho and Kowalski, tumor stage was not associated with permanent hypocalcemia [18]. In this study, although the rate of complications increased with tumor stage, this difference was not significant.

Both in our study and in a study of 34 patients with thyroiditis by Bhattacharyya and Fried, the presence of concomitant lymphocytic thyroiditis with thyroid malignancy was not a risk factor for permanent hypocalcemia [17].

Permanent hypocalcemia rates were found to be increased with reoperative thyroid surgery and neck dissection with thyroidectomy. Other risk factors were; hyperthyroidism for total-subtotal thyroidectomy group, incidental parathyroidectomy for reoperative thyroid surgery group, and extrathyroidal soft tissue invasion for neck dissection with or without thyroidectomy group.

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