World J Surg (2019) 43:1728–1735
https://doi.org/10.1007/s00268-019-04987-z

ORIGINAL SCIENTIFIC REPORT

Hypoparathyroidism After Total Thyroidectomy: Importance of the Intraoperative Management of the Parathyroid Glands

Guillermo Ponce de León-Ballesteros[1] · David Velázquez-Fernández[1] · F. Javier Hernández-Calderón[1] · Carlos Bonilla-Ramírez[1] · Rafael H. Pérez-Soto[1] · Juan Pablo Pantoja[1] · Mauricio Sierra[1] · Miguel F. Herrera[1]

Published online: 27 March 2019

Abstract

Background Total thyroidectomy is the most common surgical procedure for the treatment of thyroid diseases. Postoperative hypocalcemia/hypoparathyroidism is the most frequent complication after total thyroidectomy. The aim of this study was to evaluate the rate of postoperative hypocalcemia and permanent hypoparathyroidism after total thyroidectomy in order to identify potential risk factors and to evaluate the impact of parathyroid autotransplantation.

Patients and Methods We performed a retrospective analysis of 1018 patients who underwent total thyroidectomy at our institution between 2000 and 2016. Medical records were reviewed to analyze patient features, clinical presentation, management and postoperative complications. Descriptive and inferential statistics were employed based on the natural scaling of each included variable. Statistical significance was set at $p \leq 0.05$.

Results Mean ± SD age was 46.79 ± 15.9 years; 112 (11.7%) were males and 844 (88.3%) females. A total of 642 (67.2%) patients underwent surgery for malignant disease. The rate of postoperative hypocalcemia, transient, protracted and permanent hypoparathyroidism was 32.8%, 14.43%, 18.4% and 3.9%, respectively. Permanent hypoparathyroidism was significantly associated with the number of parathyroid glands remaining in situ (4 glands: 2.5%, 3 glands: 3.8%, 1–2 glands: 13.3%; $p < 0.0001$) [OR for 1–2 glands in situ = 5.32, CI 95% 2.61–10.82]. Other risk factors related to permanent hypoparathyroidism were obesity (OR 3.56, CI 95% 1.79–7.07), concomitant level VI lymph node dissection (OR 3.04, CI 95% 1.46–6.37) and incidental parathyroidectomy without autotransplantation (OR 3.6, CI 95% 1.85–7.02).

Conclusions Identification and in situ preservation of at least three parathyroid glands were associated with a lower rate of postoperative hypocalcemia (30.4%) and permanent postoperative hypoparathyroidism (2.79%).

Introduction

Total thyroidectomy (TT) is the most common surgical procedure for the treatment of thyroid cancer, goiter and nodules suspicious of malignancy [1]. Leading complications related to TT are vocal cord palsy, bleeding and postoperative hypocalcemia, which is the most common one. Reported ranges of transient and permanent hypoparathyroidism are 1.6–60% and ≤1 and 32%, respectively, [1–3]. In one recent study from the British Association of Endocrine and Thyroid Surgeons, Chadwick

✉ Miguel F. Herrera
miguelfherrera@gmail.com

[1] Service of Endocrine and Advanced Laparoscopic Surgery/ Department of Surgery, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubiran, Vasco de Quiroga 15, Seccion XVI, Tlalpan, 14000 Mexico City, Mexico

et al. reported a prevalence of persistent hypoparathyroidism of 7.3% [4].

Postoperative hypoparathyroidism is a consequence of a decline in circulating PTH, due to the decrease in the total volume of the functioning parathyroid parenchyma related to intraoperative ischemia or resection of one or more parathyroid glands [5–7].

Strategies to prevent permanent hypoparathyroidism include preservation of parathyroid glands through meticulous dissection and preservation of their blood supply and parathyroid gland autologous transplantation or autotransplantation [6–11]. Although the latter has shown effectiveness in 55–100% of the cases, previous studies have demonstrated that an important factor for postoperative normocalcemia is the preservation of at least three parathyroid glands in situ [2–4, 12, 13].

Several studies have demonstrated that grafted parathyroid cells show regeneration and indirect signs of activity 2 weeks after transplantation [10, 11, 14]. However, some authors have questioned the benefit of autotransplanting parathyroid glands, since patients experience similar rates of permanent hypoparathyroidism to non-transplanted subjects [6, 10, 15].

The aims of the current study were: (1) to determine the rate of postoperative hypocalcemia and permanent hypoparathyroidism in our institution; (2) to identify their risk factors; and 3) to evaluate the impact of parathyroid autotransplantation.

Patients and Methods

We performed a retrospective analysis of 1018 patients who underwent initial TT at our institution from January 2000 to December 2016. Our Institutional Review Board approved the study (CIBH 2408). Exclusion criteria were less than TT, reoperative surgery, concomitant parathyroidectomy due to hyperparathyroidism, incomplete medical record, patients receiving oral calcium supplementation due to other causes and one patient with no parathyroid gland preserved in situ. Therefore, 956 patients were finally included for definitive analysis. All patients had at least one year of clinical follow-up.

Symptoms suggestive of hypocalcemia, and levels of serum calcium and phosphate were obtained and recorded 24 h after surgery in all cases. Postoperative parathyroid hormone (PTH) levels were determined only when there was a suspicion of hypoparathyroidism. Postoperative hypocalcemia was defined as a serum calcium level of less than 8 mg/dL, 24 h after TT. Protracted hypoparathyroidism (PrHP) was considered when patients received calcium supplementation and/or had a PTH level below 13 after 1 month but less than 12 months. Permanent hypoparathyroidism (PtHP) was defined as the need for calcium supplementation with or without active vitamin D and/or magnesium to achieve normal calcium levels for more than 12 months. Symptomatic patients requiring calcium supplementation were also included in the study regardless of the PTH values [16].

In patients with serum calcium below 8 mg/dL and/or associated symptoms, IV or oral calcium was administered. In those patients with serum calcium between 8 and 8.6 mg/dL, prophylactic oral calcium supplementation was prescribed before discharge. Calcium supplementation doses were adjusted during follow-up according to symptoms and serum calcium levels. In almost all patients, renal function and urinary calcium excretion were monitored. In 30 (81%) of the 37 patients, a vitamin D analog was also administered, with an average dose of 0.35 µg/d (0.25–1 µg/d). In addition, one-third of the patients received a thiazide diuretic. PTH levels were measured selectively before 2017 and routinely thereafter.

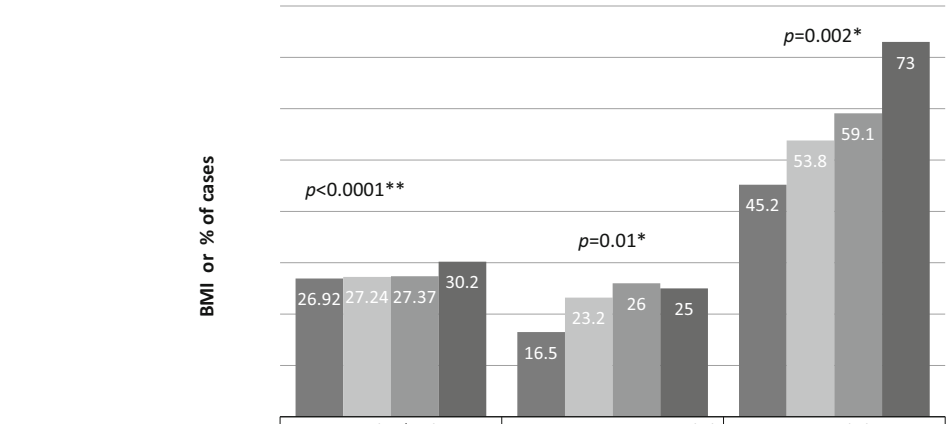
Four surgeons performed or supervised all procedures. Attempts to identify and preserve all parathyroid glands in situ in all patients were made. When a parathyroid gland was non-viable or resected unintentionally, it was generally autotransplanted into the ipsilateral sternocleidomastoid muscle after histological confirmation by an intraoperative frozen section. For autotransplantation, parathyroid glands were fragmented into 1-mm pieces and inserted into 3–4 muscular pouches.

The number of parathyroid glands resected, autografted, identified and preserved in situ was recorded in all cases. Patients were classified into five groups as shown in Table 1 according to the number of parathyroid glands preserved in situ and the number of autografted parathyroid glands. Also, the PGRIS score was used to classify the patients [8]. For the analysis of potential risk factors for PtHP, the following elements were included: older age (≥65 years), obesity, malignancy, tumor size, extracapsular extension, extension of surgery, number of parathyroid glands preserved in situ, parathyroid autotransplantation as well as other relevant surgical variables such as operative time and estimated blood loss.

Statistical analysis was performed using the IBM® SPSS® Statistics software version 24.0 (IBM Corp., Armonk, New York, USA). Distribution shape, kurtosis and skewness were reviewed in all included variables separately. Descriptive and inferential statistics were employed based on the inherent scaling of the analyzed variables. ANOVA and unpaired Student's *t*-test were used for quantitative variables. Pearson's Chi-square test or Fisher's exact test was used for categorical variables. Additionally, multivariable statistical analysis was performed by means of binomial logistic regression analysis with conditional, LR and Wald forward stepwise methods

Table 1 Parathyroid gland management groups

Group	Definition
1	At least 4 parathyroid glands preserved in situ
2	3 parathyroid glands preserved in situ and 1 autografted
3	3 parathyroid glands preserved in situ and 1 resected
4	1–2 parathyroid glands preserved in situ and at least 1 autografted
5	1–2 parathyroid glands preserved in situ and at least 2 resected and none autografted



	BMI (Kg/m2)	Metastasis at diagnosis (%)	CCND (%)
Normocalcemic patients	26.92	16.5	45.2
Postoperative Hypocalcemia	27.24	23.2	53.8
Protracted hypoparathyroidism	27.37	26	59.1
Permanent hypoparathyroidism	30.2	25	73

*: Pearson´s X^2, **: ANOVA test

Fig. 1 Comparison of clinicopathological variables among postoperative normocalcemic and hypocalcemic patients, patients with protracted hypoparathyroidism and permanent hypoparathyroidism. *Pearson's Chi-square test, **ANOVA test

used for assessing the risk factors for permanent hypoparathyroidism. Statistical significance was set at $p \leq 0.05$ or 5% (alpha error) for a two-tailed hypothesis test.

Results

Mean ± SD age of the 956 patients was 46.79 ± 15.9 years (range 11–88). There were 844 [88.3%] women and 112 [11.7%] men. Thyroid cancer was the definitive diagnosis in 642 patients (67.2%), multinodular goiter in 214 (22.4%), follicular adenoma in 41 (4.3%), Graves' disease in 28 (2.9%), and Hashimoto thyroiditis in 25 (2.6%), and other diagnosis was established in six (0.6%). Central neck lymph node dissection was performed in 459 (48%) patients. Mean ± SD operative time was 187.1 ± 67.9 min, whereas estimated blood loss was 136.5 ± 286.6 cc.

All included patients had a mean ± SD clinical follow-up of 72.7 ± 52.3 months after surgery. Postoperative hypocalcemia (<8 mg/dL) was observed in 314 (32.8%) patients. A group of 138 (43.9%) of these patients recovered during the first postoperative month with a rate of transient hypoparathyroidism of 14.4%. The rate of protracted (PrHP) and permanent (PtHP) hypoparathyroidism was 18.4% (176/956) and 3.9% (37/956), respectively. Significant differences in clinicopathological and perioperative characteristics between patients with postoperative normocalcemia, PrHP and PtHP are shown in Figs. 1 and 2. There was no difference in mean age, gender, final diagnosis (benign vs. cancer), tumor size or extracapsular extension among groups.

Oral calcium supplementation was administered to 396 (41.4%) patients, and 158 (16.5%) required intravenous calcium infusion followed by oral supplementation. Mean ± SD dose of oral calcium carbonate per day in the first postoperative week was 4.1 ± 7.7 g (range 0–93), at one month 2.66 ± 7.4 g (range 0–93), at 3 months 1.73 ± 5.8 g (range 0–54), at 6 months 1.24 ± 4.9 g (range 0–60) and at 1 year 0.83 ± 4.6 g (range 0–60). Comparison of serum calcium levels at 24 h, 1 month, 6 and 12 months in patients with postoperative hypocalcemia, PrHP and PtHP demonstrated a significant difference between groups ($p = 0.0001$). IV calcium during the

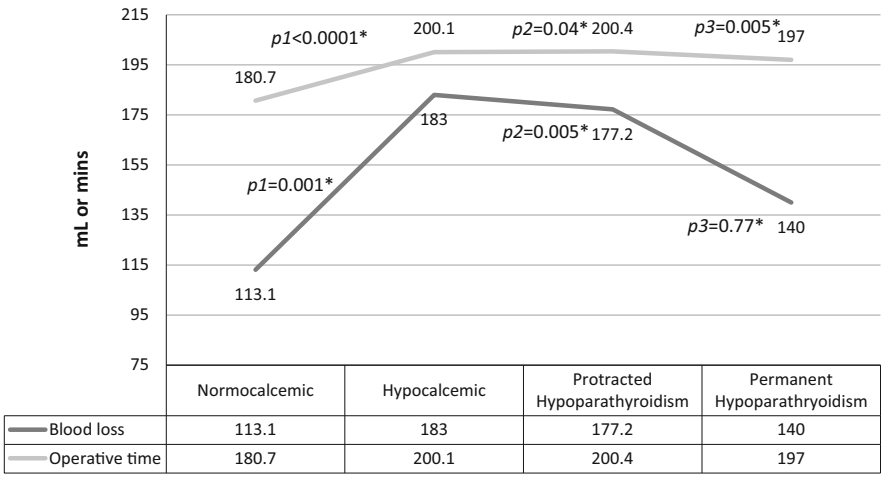


Fig. 2 Comparison of perioperative variables among the following postoperative groups: patients with normocalcemia, hypocalcemia, protracted hypoparathyroidism and permanent hypoparathyroidism. *p*1 Comparison between normocalcemic patients and patients with postoperative hypocalcemia; *p*2 comparison between patients with protracted hypoparathyroidism and normocalcemic or recovered patients; *p*3 comparison between patients with permanent hypoparathyroidism and normocalcemic or recovered patients. * ANOVA test

first 48 postoperative hours was administered in 127 (40.4%) patients with postoperative hypocalcemia, whereas in patients with protracted and permanent hypoparathyroidism, it was administered in 99 (56.3%) and 31 (83.8%), respectively, with an OR of 32.39 (CI 95% 13.25–79.21; p <0.0001). In the groups of patients with protracted and permanent hypoparathyroidism, mean calcium oral supplementation dosage at 1 year was 0.3 ± 1.2 and 19.2 ± 12.8 grams per day, respectively. Thiazide diuretics were used in 11 (28.9%), while 30 (81%) of the patients with permanent hypoparathyroidism used vitamin D analogs; mean calcitriol and cholecalciferol dosage was 0.35 ± 0.19 µg/d and 1272.72 ± 1005.1 ID/d, respectively. No patient used rhPTH.

The incidence of postoperative hypocalcemia, PrHP and PtHP according to the number of parathyroid glands left in situ and the usage of parathyroid autotransplantation are shown in Table 2 and according to PGRIS score in Table 3.

The analysis of potential risk factors for postoperative hypocalcemia, PrHP and PtHP is shown in Table 4. According to parathyroid autotransplantation, PrHP had an OR of 1.66 (CI 95% 1.06–2.59; $p = 0.032$) and PtHP had an OR of 1.99 (95% IC 0.88–4.45; $p = 0.08$). Parathyroid autotransplantation in patients with at least one resected parathyroid gland showed an OR of 1.06 to PrHP (95% IC 0.63–1.8; $p = 0.8$) and an OR of 0.95 to PtHP (CI 95% 0.38–2.38; $p = 0.92$).

Multivariable logistic regression analysis by a conditional, LR and Wald forward stepwise models demonstrated that the preservation of ≤2 parathyroid glands in situ ($p < 0.0001$), obesity ($p < 0.0001$) and central

Table 2 Comparison between parathyroid glands management groups

Group		*n* (%)	Postoperative hypocalcemia *n* (%)	Protracted hypoparathyroidism *n* (%)	Permanent hypoparathyroidism *n* (%)
1	At least 4 parathyroid glands preserved in situ	649 (67.9)	193 (29.7)	99 (15.3)	16 (2.5)
2	3 parathyroid glands preserved in situ and 1 autografted	82 (8.6)	24 (29.3)	16 (19.5)	3 (3.7)
3	3 parathyroid glands preserved in situ and 1 resected	127 (13.3)	44 (34.6)	25 (19.7)	5 (3.9)
4	1–2 parathyroid glands preserved in situ and at least 1 autografted	38 (4)	25 (65.8)	15 (39.5)	5 (13.2)
5	1–2 parathyroid glands preserved in situ and at least 2 resected. No parathyroid gland autografted	60 (6.3)	28 (46.7)	21 (35)	8 (13.3)
			$p \leq 0.0001$*	$p \leq 0.0001$*	$p \leq 0.0001$*

**P* value Pearson's Chi-square test. Comparison between group rates

Table 3 Rate of postoperative hypocalcemia, protracted and permanent hypoparathyroidism according PGRIS score

Group		*n* (%)	Postoperative hypocalcemia *n* (%)	Protracted hypoparathyroidism *n* (%)	Permanent hypoparathyroidism *n* (%)
1	PGRIS score 4	649 (67.9)	193 (29.7)	99 (15.3)	16 (2.5)
2	PGRIS score 3	209 (21.9)	68 (32.5)	41 (19.6)	8 (3.8)
3	PGRIS score 1–2	98 (10.3)	53 (54.1)	36 (36.7)	13 (13.3)
			$p \leq 0.0001$*	$p \leq 0.0001$*	$p \leq 0.0001$*

**P* value Pearson's Chi-square test. Comparison between group rates

compartment lymph node dissection ($p = 0.015$) were significantly related to PtHP.

Discussion

Postoperative hypocalcemia and PrHP are the most common complications after total thyroidectomy, with highly published ranges from 1.6 to 60% and ≤1 to 32%, respectively, [1–3, 17]. PtHP has been traditionally associated with short- and long-term sequelae, including hypocalcemic and/or hypercalcemic crises, hyperphosphatemia, gastrointestinal and neuropsychiatric symptoms, cataracts, frequent infections and renal failure [17–19].

Some authors have described different strategies to prevent PtHP in total thyroidectomized patients. These include meticulous dissection with isolation and individual control of all arteries and veins in order to preserve well-vascularized parathyroid glands. Parathyroid autotransplantation, on the other hand, has demonstrated a high-to-moderate successful rate in some international series [7, 9–11, 20].

For surgeons committed to identifying all parathyroid glands, the use of magnification lenses may help to reduce the risk of incidental parathyroidectomy. Pata et al. demonstrated that the use of magnification lenses diminished the risk of incidental parathyroidectomy from 7.8 to 3.8%. These authors also demonstrated that the rate of postoperative hypocalcemia reduced from 33.9 to 20.6% [21].

Due to the high frequency of inferior parathyroid glands in an unusual anatomic location, identification of all glands may require extensive dissection [22]. As a consequence of this statement, some authors such as Song et al. have suggested that preserving one parathyroid gland with an intact blood supply might be sufficient to prevent PtHP [23].

Since 1973, several studies have demonstrated that parathyroid autotransplantation is a useful strategy to prevent postoperative hypoparathyroidism [10, 24]. However, it has been recently questioned by some authors. For instance, Lorente-Poch et al. demonstrated that it did not influence the rate of PtHP after total thyroidectomy, with a rate of 5.3% in patients with incidental parathyroidectomy without autotransplantation and 7.3% in patients with parathyroid autotransplantation [6].

Some risk factors related to PtHP in total thyroidectomy include concomitant central neck lymph node dissection, diagnosis of thyroid malignancy, young age, female gender, vitamin D deficiency, autoimmune thyroid disease, concomitant parathyroidectomy (including biopsies during surgery), reoperative surgery and the number of functioning parathyroid glands remaining in situ [1, 2, 17, 25]. PtHP in our series was 3.9%, being the most important protective factor for the preservation of >2 parathyroid glands (OR 5.31, CI 95% 2.61–10.82). When at least three glands were left in situ, the rate of PtHP fluctuated from 2.5 to 3.8%, but when ≤2 were preserved in situ, this rate increased up to 13.3%. Other related risk factors were obesity (OR 3.55; CI 95% 1.79–7.07; $p < 0.0001$), concomitant central neck lymph node dissection (OR 3.04; CI 95 1.46–6.36; $p = 0.002$) and incidental parathyroidectomy (non-autotransplanted) (OR 3.6; CI 95% 1.85–7.02; $p < 0.0001$). Gender, malignancy, autoimmune disease and tumor size did not show any statistical significance in our study, in contrast to other published series.

In a study published by Lorente-Poch et al. of 657 patients who underwent total thyroidectomy, the rate of PtHP was 16% when ≤2 parathyroid glands were left in situ, whereas it was 6.5% in patients with three glands remaining in situ and 2.6% in patients with their four glands preserved in situ [8]. In a multicenter study, Thomusch et al. reported that the resection of at least 2 parathyroid glands increased the risk of transient and permanent hypothyroidism, with an OR of 1.4 and 4.1 respectively, section of the inferior thyroid artery and the extent of thyroid resection were the second and third most relevant risk factors for PtHP [26]. Their results differ from our study, as no difference between preserving two or three parathyroid glands in situ was found.

Obesity was one of the related risk factors for PtHP in our series, without a clear explanation. Patients with obesity may have an increased risk of incidental parathyroidectomy due to the increased amount of cervical fat.

Table 4 Risk factors related to postoperative hypocalcemia, protracted and permanent hypoparathyroidism after total thyroidectomy

Variables	Total $n = 956$	Normocalcemic patients $n = 642$	Postoperative hypocalcemia $n = 314$	$p1$	Protracted hypoparathyroidism $n = 176$	$p2$	Permanent hypoparathyroidism $n = 37$	$p3$
Age > 65 years, *n* (%)	130 (13.6)	73 (11.4)	57 (18.2)	0.005*	29 (16.5)	0.30*	4(10.8)	0.55*
BMI ≥ 30 kg/m^2, *n* (%)	249 (26)	162 (25.2)	87 (27.7)	0.63*	55 (31.25)	0.15*	20 (54)	0.0001*
Metastasis at diagnosis, *n* (%)	177 (18.5)	105 (16.4)	72 (22.9)	0.013*	45 (25.6)	0.009*	9 (24.3)	0.32*
TT + CCND, *n* (%)	459 (48)	290 (45.2)	169 (53.8)	0.012*	104 (59)	0.001*	27 (72.9)	0.002*
Graves' disease, *n* (%)	28 (2.9)	22 (3.4)	6 (1.9)	0.19*	4 (2.3)	0.8*	0	0.62*
Number of parathyroid glands in situ								
4, *n* (%)	649 (67.9)	456 (70.2)	193 (29.7)	0.002*	99 (15.3)	0.0001*	16 (2.5)	0.001*
3, *n* (%)	209 (21.9)	141 (67.5)	68 (32.5)	0.91*	41 (19.6)	0.61*	8 (3.8)	0.97*
≤2, *n* (%)	98 (10.3)	45 (45.9)	53 (54.1)	0.0001*	36 (36.7)	0.0001*	13 (13.3)	0.0001*
Incidental parathyroidectomy, *n* (%)	192 (20.1)	108 (56.3)	84 (43.7)	0.0001*	56 (29.2)	0.0001*	17 (8.9)	0.0001*
Parathyroid autotransplantation, *n* (%)	120 (12.5)	71 (59.2)	49 (40.8)	0.046*	31 (25.8)	0.025*	8 (6.7)	0.089*

$p1$ Comparison between normocalcemic patients and patients with postoperative hypocalcemia, $p2$ comparison between patients with protracted hypoparathyroidism and normocalcemic or recovered patients, $p3$ comparison between patients with permanent hypoparathyroidism and normocalcemic or recovered patients

BMI body mass index, *TT* total thyroidectomy, *CCND* central compartment node dissection

*Pearson's Chi-square test

However, in our series, the rate of inadvertent parathyroidectomy was similar in patients with (20.1%) and without obesity (20%) ($p = 0.98$). Another possible explanation could be a higher incidence of vitamin D deficiency in patients with obesity, which has been reported as high as 35% [27]. The recommendation to measure 25-hydroxy vitamin D levels in addition to Ca and PTH has been made. Proper vitamin D supplementation prior to a total thyroidectomy is highly recommended, especially in those patients with severe (<10 ng/mL) and moderate (10 to <20 ng/mL) vitamin D deficiency [28].

It has been widely demonstrated that incidental parathyroidectomy is more frequent in patients with concomitant central compartment lymph node dissection, with a reported frequency close to 30%. The rate of PtHP in patients with inadvertent parathyroidectomy is close to 6% [1]. In our series, the rate of PtHP in patients with incidental parathyroidectomy was 8.9%, while in patients without incidental parathyroidectomy, it was only 2.6%. Incidental parathyroidectomy was also more frequent in patients undergoing concomitant central compartment lymph node dissection, with a rate of 24.5% compared to 16.1% in the group that did not have central compartment lymph node dissection, which gives an OR of 1.68 (CI 95% 1.22–2.32; $p = 0.001$). It is also widely known that lymph node dissection of the central compartment increases the risk of impaired blood supply of parathyroid tissue. According to this, Orloff et al. suggested that central compartment lymph node dissection ipsilateral to primary thyroid cancer should be performed first and then that the decision of completing the bilateral central dissection should be established balancing the potential oncological benefit versus the risk of postoperative hypoparathyroidism [28].

There is some controversy whether parathyroid glands with some degree of ischemia should be left in situ or resected and autotransplanted. Promberger et al. suggested that only parathyroid glands with clear evidence of ischemia should be resected and autotransplanted, as patients with mild discolored parathyroid glands left in place may have faster normalization of PTH levels and a lower rate of PrHP compared to those patients who underwent parathyroid autotransplantation [29].

In our series, the incidence of PrHP was 25.8% in patients with parathyroid autotransplantation, while in patients without parathyroid autotransplantation, it was 17.3% (OR 1.66; $CI_{95\%}$ 1.06–2.59; $p = 0.025$). The incidence of permanent hypoparathyroidism was also higher in patients with parathyroid autotransplantation, 6.7% (8/120) vs 3.5% (29/836), although without statistical significance ($p = 0.089$). Our figures are close to 7.3% and 5.3% reported by Lorente-Poch et al. in a similar comparison [6]. Kirdak et al. found a higher difference between patients undergoing parathyroid autotransplantation (11.5%) and glands left in situ (3.3%) [30].

The present study has some limitations such as its retrospective nature and the absence of an objective evaluation of the autotransplanted parathyroid tissue. Another limitation was the lack of routine PTH and vitamin D measurements. They were determined only when there was suspicion of hypoparathyroidism. These might reduce the statistical power of our inferential assumptions, increasing the harboring of a type II error.

Conclusions

Appropriate intraoperative parathyroid identification with in situ preservation of at least three glands might be the most important strategy to prevent transient and permanent postoperative hypoparathyroidism. Surgeons should avoid incidental parathyroidectomy performing a meticulous surgical dissection of parathyroid glands in order to ensure their adequate vascularity and therefore their proper functionality.

References

1. Zhou HY, He JC, McHenry CR (2016) Inadvertent parathyroidectomy: incidence, risk factors, and outcomes. J Surg Res 205:70–75
2. Edafe O, Antakia R, Laskar N, Uttley L, Balasubramanian SP (2014) Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. Br J Surg 101:307–320
3. Fama F, Cicciu M, Polito F, Cascio A, Gioffre-Florio M et al (2017) Parathyroid autotransplantation during thyroid surgery: a novel technique using a cell culture nutrient solution. World J Surg 41:457–463
4. Chadwick DR (2017) Hypocalcaemia and permanent hypoparathyroidism after total/bilateral thyroidectomy in the BAETS Registry. Gland Surg 6:S69–S74
5. Asari R, Passler C, Kaczirek K, Scheuba C, Niederle B (2008) Hypoparathyroidism after total thyroidectomy: a prospective study. Arch Surg 143:132–137 **(Discussion 8)**
6. Lorente-Poch L, Sancho J, Munoz JL, Gallego-Otaegui L, Martinez-Ruiz C, Sitges-Serra A (2017) Failure of fragmented parathyroid gland autotransplantation to prevent permanent hypoparathyroidism after total thyroidectomy. Langenbeck's Arch Surg 402:281–287
7. Shaha AR, Jaffe BM (1998) Parathyroid preservation during thyroid surgery. Am J Otolaryngol 19:113–117
8. Lorente-Poch L, Sancho JJ, Ruiz S, Sitges-Serra A (2015) Importance of in situ preservation of parathyroid glands during total thyroidectomy. Br J Surg 102:359–367
9. Herrera M, Grant C, van Heerden JA, Fitzpatrick LA (1992) Parathyroid autotransplantation. Arch Surg 127:825–829 **(Discussion 9–30)**
10. Sierra M, Herrera MF, Herrero B, Jimenez F, Sepulveda J et al (1998) Prospective biochemical and scintigraphic evaluation of

autografted normal parathyroid glands in patients undergoing thyroid operations. Surgery 124:1005–1010
11. Wells SA Jr, Gunnells JC, Shelburne JD, Schneider AB, Sherwood LM (1975) Transplantation of the parathyroid glands in man: clinical indications and results. Surgery 78:34–44
12. Su A, Gong Y, Wu W, Gong R, Li Z, Zhu J (2018) Does the number of parathyroid glands autotransplanted affect the incidence of hypoparathyroidism and recovery of parathyroid function? Surgery 164:124–129
13. Sitges-Serra A, Ruiz S, Girvent M, Manjon H, Duenas JP, Sancho JJ (2010) Outcome of protracted hypoparathyroidism after total thyroidectomy. Br J Surg 97:1687–1695
14. Lo CY, Lam KY (2001) Routine parathyroid autotransplantation during thyroidectomy. Surgery 129:318–323
15. Tartaglia F, Blasi S, Giuliani A, Merola R, Livadoti G et al (2016) Parathyroid autotransplantation during total thyroidectomy. Results of a retrospective study. Int J Surg 28(Suppl 1):79–83
16. Lorente-Poch L, Sancho JJ, Munoz-Nova JL, Sanchez-Velazquez P, Sitges-Serra A (2015) Defining the syndromes of parathyroid failure after total thyroidectomy. Gland Surg 4:82–90
17. Stack BC Jr, Bimston DN, Bodenner DL, Brett EM, Dralle H et al (2015) American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: postoperative hypoparathyroidism-definitions and management. Endocr Pract Off J Am Coll Endocrinol Am Assoc Clin Endocrinol 21:674–685
18. Underbjerg L, Sikjaer T, Rejnmark L (2018) Long-term complications in patients with hypoparathyroidism evaluated by biochemical findings: a case-control study. J Bone Miner Res Off J Am Soc Bone Miner Res 33:822–831
19. Lorente-Poch L, Sancho JJ, Carballo L, Sitges-Serra A (2017) Clinical profile and long-term follow-up of 32 patients with postoperative permanent hypoparathyroidism. Gland Surg 6:S3–S10
20. Wells SA Jr, Burdick JF, Hattler BG, Christiansen C, Pettigrew HM et al (1974) The allografted parathyroid gland: evaluation of function in the immunosuppressed host. Ann Surg 180:805–813
21. Pata G, Casella C, Mittempergher F, Cirillo L, Salerni B (2010) Loupe magnification reduces postoperative hypocalcemia after total thyroidectomy. Am Surg 76:1345–1350
22. Chang YK, Lang BHH (2017) To identify or not to identify parathyroid glands during total thyroidectomy. Gland Surg 6:S20–S29
23. Song CM, Jung JH, Ji YB, Min HJ, Ahn YH, Tae K (2014) Relationship between hypoparathyroidism and the number of parathyroid glands preserved during thyroidectomy. World J Surg Oncol 12:200
24. Wells SA Jr, Burdick JF, Christiansen CL, Abe M, Sherwood LM et al (1973) Long-term survival of dogs transplanted with parathyroid glands as autografts and as allografts in immunosuppressed hosts. Transpl Proc 5:769–771
25. Lefevre JH, Tresallet C, Leenhardt L, Jublanc C, Chigot JP, Menegaux F (2007) Reoperative surgery for thyroid disease. Langenbeck's Arch Surg 392:685–691
26. Thomusch O, Machens A, Sekulla C, Ukkat J, Brauckhoff M, Dralle H (2003) The impact of surgical technique on postoperative hypoparathyroidism in bilateral thyroid surgery: a multivariate analysis of 5846 consecutive patients. Surgery 133:180–185
27. Pereira-Santos M, Costa PR, Assis AM, Santos CA, Santos DB (2015) Obesity and vitamin D deficiency: a systematic review and meta-analysis. Obes Rev Off J Int Assoc Study Obes 16:341–349
28. Orloff LA, Wiseman SM, Bernet VJ, Fahey TJ 3rd, Shaha AR et al (2018) American Thyroid Association Statement on Postoperative Hypoparathyroidism: diagnosis, prevention, and management in adults. Thyr Off J Am Thyr Assoc 28:830–841
29. Promberger R, Ott J, Kober F, Mikola B, Karik M et al (2010) Intra- and postoperative parathyroid hormone-kinetics do not advocate for autotransplantation of discolored parathyroid glands during thyroidectomy. Thyr Off J Am Thyr Assoc 20:1371–1375
30. Kirdak T, Dundar HZ, Uysal E, Ocakoglu G, Korun N (2017) Outcomes of parathyroid autotransplantation during total thyroidectomy: a comparison with age- and sex-matched controls. J Invest Surg 30:201–209