

INCIDENTAL PARATHYROIDECTOMY DURING TOTAL THYROIDECTOMY AS A POSSIBLE RISK FACTOR OF HYPOCALCEMIA. EXPERIENCE OF A SINGLE CENTER AND REVIEW OF LITERATURE

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Abstract

Context. Post-operative clinical and biochemical hypocalcemia is a common complication of thyroid surgery and the correlation with incidental parathyroidectomy (IP) remains controversial.

Objective. To evaluate the incidence of IP during TT, its correlation to early post-surgery hypocalcemia, and its potential risk factors.

Patients and Methods. 77 consecutive patients submitted to thyroid surgery between January 2018 and December 2019. Demographic, clinical, biochemical, surgical and histopathological factors were assessed. Statistical multivariate analysis was performed to identify the risk of IP.

Results. IP was evident in 22 (28.5%) patients who underwent TT, TT with lymph node dissection of the central compartment (CLND) and reoperation for previous hemithyroidectomy with CLND. Early symptomatic hypocalcemia 24 hours after TT was demonstrated in 12/22 (54.5%) patients, with PTH value of <14pg/mL in 7/12 (58.3%) patients, and in 6 of these 7 patients (85.7%) the PTH value was <6.3pg/mL. In 5/22 (22.7%) patients the IP was associated with biochemical hypocalcemia <8.4mg/dL, and in 5/22 (22.7%) patients anatomical damage was not associated with a reduction in plasma calcium levels. The severity of early post-op hypocalcemia was not correlated with the number of parathyroid glands left *in situ*. The multivariate analysis did not show statistically significant values between the clinical-pathological variables and increased risk of IP.

Conclusions. No IP clinical-pathological risk factors have been identified during thyroid surgery. In all cases of TT, with or without CLND, the meticulous identification of the parathyroid glands, whose incidental removal is frequently associated with clinical and biochemical hypocalcemia, is recommended.

Keywords: Incidental Parathyroidectomy, Thyroidectomy, Hypocalcemia.

INTRODUCTION

Post-operative (post-op) clinical and biochemical hypocalcemia is a common complication of thyroid surgery. In several studies this condition has been temporary and persistent with an incidence of 42.1% and 6.7% respectively (1,2). Incidental parathyroidectomy (IP) is frequently associated with total thyroidectomy (TT) with an incidence ranging between 3.7-24.9% (1-5). The correlation of clinical and biochemical hypocalcaemia and TT remains controversial and the consequences are not completely defined (2).

In the study of Ozden *et al.* the IP was present in 5.8% of patients who underwent TT (1).

According to Lin YS, hypocalcemia is found in 6.4% of IP cases (3). Otherwise Manatakis *et al.* showed that the incidence of IP was 24.9%, with histological finding of glands in intrathyroid position in 44.3% of the patients (4). Furthermore, Neagoe *et al.* showed that the incidence of IP during open TT is like that reported in robotic or video-assisted procedures (2).

Hypoparathyroidism post-IP is significantly associated with the number of glands left *in situ*: 4 glands 2.5%, 3 glands 3.8%, 1-2 glands 13.3% (5). Significant IP risk factors are: female sex, age <28.5 years, obesity, neoplastic pathology, lymph node dissection of the central compartment (CLND), TT, reoperation (5-7).

The aims of the study were to determine the incidence of IP after TT, the relationship between IP and early post-op hypocalcemia and the potential clinical-pathological risk factors of IP.

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PATIENTS AND METHODS

Prospective observational study conducted at “A. Fiorini” hospital in Terracina UOC University Surgery, Faculty of Pharmacy and Surgery-Polo Pontino,” Sapienza” University of Rome. The study was performed in accordance with the principles of the Helsinki Declaration.

The study included 77 patients, 57 female (mean age 57.1 ± 13.9 SD, range 31-78 years), 20 male (mean age 56.8 ± 12.0 SD, range 30-75 years) enrolled in the period between January 2018 - December 2019 underwent TT or completion of previous open hemithyroidectomy.

In all cases, the indication for surgical treatment was determined by endocrinologists. The following factors were assessed: sex, age, BMI, alcohol consumption, habitual smoking, comorbidity, cytological examination with ultrasound-guided fine needle aspiration (FNAC), ASA score, indication on intervention, duration of anesthesia and surgery, surgical procedure adopted, organ volume, symptoms of hypocalcemia, histopathological findings, extra-capsular and intra-capsular number and localization of incidentally removed parathyroid glands, serum calcium levels (vn $8.4-10.2$ mg/dL), parathyroid hormone (PTH) (vn $14-80$ pg/mL) in pre-op and in day I, II, III post-op during hospitalization, and in day IV, V post-op after discharge in continuity of care.

The study included the following exclusion criteria: ASA Score > III sec by the American Society of Anesthesiologists, age <18 years and > 85 years, antibiotic therapy performed within 15 days before surgery, psychiatric disorders causing non-cooperation, history of alcohol abuse and drug addiction, pregnancy, breastfeeding, refusal to subscribe informed consent, chronic steroid use, chemotherapy for malignant disease within 30 days before surgery, radiotherapy for malignant disease within 90 days before surgery, history of cardiac surgery, severe congestive heart failure and chronic obstructive pulmonary disease (COPD) and patients in dialysis.

Patients were subjected pre-op to ENT evaluation and fibrolaryngoscopy with a flexible instrument to exclude motor dysfunction of the vocal cords (TVC). The surgery was performed under general anesthesia, by surgeons who are experienced in the procedure, and involved mobilizing the patient 6-8 hours after the thyroidectomy. Local hemostats, bipolar and US scalpels (Harmonic Focus®) were used during the surgical procedure. In all cases, two suction drains

were positioned and then removed after 72 hours.

The histological examination for the diagnosis of the nature of the thyroid disease and the identification of parathyroid glands, when incidentally removed, was always performed by the same two histologists. The patients were discharged on day III post-op and underwent outpatient follow-up at 7 and 30 days. During hospital stay, in the event of post-op hypocalcaemia associated with clinical symptoms, calcium gluconate infusions were administered as clinically indicated, in the event of post-op subclinical hypocalcaemia calcium implementations and calcitriol were administered orally to raise serum calcium; in both cases oral therapy was continued at home after discharge, and serum levels of calcium and PTH were checked in continuity of care.

The serum calcium level was evaluated corrected with albumin (cCa) and oral therapy was administered daily as follows: if $cCa > 8.5$ mg/dL and $PTH > 17-20$ pg/mL no therapy was needed; if $cCa 8-8.5$ mg/dL and $PTH < 17-20$ pg/mL, calcitriol 0.5mcg and calcium Sandoz® 1000mg one time a day; if $cCa 7.5-8$ mg/dL and $PTH < 17-20$ pg/mL, calcitriol 0.5 mcg and calcium Sandoz® 1000mg two times a day; if $cCa < 7.5$ mg/dL and $PTH < 17-20$ pg/mL calcitriol 0.5 mcg and calcium Sandoz® 1000mg three times a day.

The data was collected and processed using IBM SPSS v.23.0 software. Statistical significance was set at $p < 0.05$.

The demographic and clinical characteristics of the sample are shown in Table 1.

RESULTS

IP was found in 22/77 (28.5%) patients (pts) of whom 17/22 (77%) underwent TT, 1 patient (pt) underwent completion of previous hemithyroidectomy with CLND and 4 pts underwent TT with CLND. The indication for thyroidectomy was represented by multinodular goiter in 19/22 (86%) pts. The characteristics of the incidentally removed parathyroid glands, PTH value and hypocalcemia are shown in Table 2.

In patients with IP at histological examination, multinodular hyperplasia was found in 19/22(86%) pts, associated with chronic lymphocytic thyroiditis (Hashimoto's disease) in 5/19 (26.3%) pts, isolated chronic lymphocytic thyroiditis in 1/22(4.5%) pt, follicular adenoma in 1/22 (4.5%) pt and papillary carcinoma in 3/22 (13.6%) pts.

The histological incidence of incidentally

Table 1. Demographic and clinical characteristics of the sample, with P value risk factors for IP at multivariate analysis

Parameter	n. pts (total sample 77 pts)	P value
Gender	F/M 57/20	p=0.33
Age (years)	F: 57.1±13.9 (31-78) M: 56.8± 12 (30-75)	p=0.399
BMI		
Normal	29	p=0.18
Overweight	27	
Obese	21	
Smoking habit	28	p=0.23
Alcohol habit	16	p=0.36
Comorbidity		
Hypertension	35	
Cancer	15	
Diabetes mellitus	13	
Vasculopathy	12	
COPD	10	
Heart disease	7	
Hepatic disease	6	
Renal disease	3	
Multiple sclerosis	1	
ASA score		
I	10	
II	56	
III	11	
Indication for surgery		
Multinodular goiter	77	p=0.27
Non-toxic	58	
Toxic	19	p=0.50
Intrathoracic goiter	10	
Surgical Procedures		
TT	72	p=0.135
TT with CLND	11	
Completion	5	
FNAC TIR		
I	4	p=0.612
II	21	
III A-B	12	
IV	1	
V	1	
Duration of Anesthesia	(minutes)	
average	100	p=0.68
range	60-140	
Duration of Surgery	(minutes)	
average	77	p=0.35
range	40-125	
Histological examination		
Adenomas	11	p=0.24
Carcinomas	7	
I-PTMC	4	
Hashimoto's thyroiditis	22	

removed parathyroid glands was 28.5% (22/77 pts; 18F, range 32-76 years; 4M, range 51-75 years). One parathyroid was histologically identified in 15/22 (68%) pts, and two parathyroid glands in 7/22 (32%) pts.

IP was present in the right thyroid lobe in 14/22 (63.7%), in the left lobe in 3/22 (13.6%) and in both lobes in 5/22 (22.7%) pts. Parathyroid glands with an ectopic site were identified in 2/22 (9.1%) pts, intraparenchymal in 1 pt and perithyroid adipose tissue in 1 pt.

Early symptomatic hypocalcemia 24 hours after TT was present in 12/22 (54.5%) pts, with 1 parathyroid removed in 7/12 (58.3%) pts, 2 parathyroid glands removed in 5/12 (41.6%) pts, of which 7/12 (58.3%) pts showed PTH <14pg/mL, and in 6 of these 7 pts (85.7%) was found PTH levels <6.3pg/mL, with removal of 1 gland in 3 pts, 2 glands in 3 pts. In 5/22 (22.7%) pts only biochemical hypocalcemia was found with normal PTH value, 1 parathyroid removed in 4 pts, 2 parathyroid glands removed in 1 pt.

In 5/22 (22.7%) pts anatomical damage (1 parathyroid removed in 4 pts; 2 parathyroid glands removed in 1 pt) was not associated with a reduction of plasma calcium levels.

The BMI calculation showed 6/22 (27.3%) normal weight pts, 8/22 (36.4%) overweight patients and 8/22 (36.4%) obese pts. Habitual smoking and alcohol consumption involved 5/22 (22.7%) and 3/22 (13.7%) pts respectively. The average duration of anesthesia was 101 min (range 75-140) and average surgery duration was 80 min (range 55-125). Intrathoracic goiter was diagnosed in 1/22 (4.5%) pt. FNAC had been performed in 11/22 (50%) pts, who presented suspicious lesions on imaging.

At multivariate analysis the p-value was statistically not significant for all the risk factors assessed; data are shown in Table 1.

DISCUSSION

Hypoparathyroidism, in the transient, persistent and permanent varieties, is a common complication after thyroid surgery. The condition is frequently associated with hypocalcemia even if the correlation between hypoparathyroidism and low serum calcium levels is not fully clarified yet (2).

In this study, conducted on a consecutive series of patients underwent TT, multiple parameters were evaluated in order to identify possible IP risk factors. As reported by other authors, even in this study at the multivariate analysis the p-value was not statistically

Table 2. IP Group: characteristics of removed parathyroids, PTH values and hypocalcemia

IP Group (pts tot. n.22)	n. pts (%)	n.1 parathyroids removed n.pts (%)	n.2 parathyroids removed n.pts (%)
Parathyroids removed		15(68) [intracapsular 1] [extracapsular1]	7(32)
PTH value, day I p.o. (nv 14-80 pg/mL)	<14 [<6.3]	7 (32) [6 (27)]	[3(13)]
Hypocalcemia, day I p.o. Serum Calcium <8.4 (nv 8.4-10.2 mg/dL)		17(77)	
	symptomatic	12(54)	5(23)
	only biochemical	5(23)	1(4.5)
Normocalcemia, day I p.o. Serum Calcium ≥8.4 (nv 8.4-10.2 mg/dL)		5(23)	1(4.5)

IP = Incidentally removed parathyroid glands; PTH = parathyroid hormone; pts = patients; p.o. = post operative; nv = normal value.

significant for all the potential clinical-pathological risk factors assessed for IP during TT (2).

In the absence of statistically significant IP risk factors, in order to limit the incidence of this complication, the intraoperative visual identification of the parathyroid glands that must always be handled gently to ensure the anatomical integrity of the glandular vascularization remains fundamental (8).

In this study, the accurate isolation of the parathyroid glands, the use of local hemostats, the bipolar and US scalpels (Harmonic Focus®) and the improvement of the surgical team’s experience, have not contributed to limit the anatomical damage of the parathyroid glands that has been reported in 28.5% of patients. Despite the team’s experience in the surgical procedure and the non-statistical significance of the p-value, the IP was described almost exclusively during TT performed for multinodular goiter in 86% of the patients, with a significant increase in the size of the gland, more frequently of the right lobe.

In the IP patients, the addition of factors such as the increase in volume of the thyroid for multinodular hyperplasia, the oxyphil cell adenoma, the papillary carcinoma, the pre-op FNAC procedure and Hashimoto’s thyroiditis, although not statistically significant probably cause difficult intra-operative visual identification and difficult dissection of parathyroid glands with consequent increased risk of IP.

The issue of incidental removal of the ectopic parathyroid glands described in 9% of patients with intra-parenchymal and extracapsular localization in the

perithyroid adipose tissue remains still open.

In this study the correlation between serum calcium and PTH remains controversial. In fact early symptomatic hypocalcemia was found in 54.5% of patients with IP, and 58.3% of them showed PTH value <14pg/mL, while in 22.7% of patients with IP and only biochemical hypocalcemia, PTH was normal, and in 22.7% of patients with IP hypocalcemia was not found. As a result, the removal of glands in patients with or without hypocalcemia is not always associated with pathological levels of PTH.

Unlike what is reported in the literature, in this study the severity of early post-op hypocalcemia was not correlated with the number of removed parathyroid glands (1 in 7pts vs. 2 in 5 pts) (5). In fact, as reported by other authors, glandular function is not always guaranteed even in the case of surgical preservation of the parathyroid glands (9). Probably, in addition to the anatomical damage of the IP, in some of the patients an ischemic suffering from diffuse vasospasm induced by proinflammatory mediators was added in the presence of anatomical integrity of the glandular vascularization (10).

PTH control is required 6-12 months after TT because when PTH <6.3pg/mL, it is considered to be an important predictor of permanent hypocalcemia (11,12).

In conclusion, in all cases of TT, with or without CLND, the meticulous identification of the parathyroid glands is recommended as their incidental removal is frequently associated with clinical and biochemical hypocalcemia.

In our experience no IP risk factors have been identified during thyroid surgery and the incidence of glandular damage was higher than the values reported in the literature, despite the detection of parathyroid glands, the use of local hemostats, the bipolar and Harmonic Focus scalpels and the improvement of the experience of the surgical team. IP from ectopic parathyroid glands with intra-capsular localization and in the perithyroidal adipose tissue is not preventable. The correlation between IP, serum calcium and PTH remains to be defined.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Ozden S, Erdogan A, Simsek B, Saylam B, Yildiz B, Tez M. Clinical course incidental parathyroidectomy: Single center experience. *Auris Nasus Larynx*. 2018;45(3):574-577.
2. Neagoe RM, Cvasciuc IT, Muresan M, Sala DT. Incidental parathyroidectomy during thyroid surgery-risk, prevention and controversies; an evidence-based review. *Acta Endocrinol (Buchar)*. 2017;13(4):467-475.
3. Lin YS, Hsueh C, Wu HY, Yu MC, Chao TC. Incidental parathyroidectomy during thyroidectomy increases the risk of postoperative hypocalcemia. *Laryngoscope*. 2017;127(9):2194-2200.
4. Manatakis DK, Balalis D, Soulou VN, Korkolis DP, Plataniotis G, Gontikakis E. Incidental Parathyroidectomy during Total Thyroidectomy: Risk Factors and Consequences. *Int J Endocrinol*. 2016;7825305.
5. Ponce de Leon-Ballesteros G, Velazquez-Fernandez D, Hernandez-Calderon FJ, Bonilla-Ramirez C, Perez-Soto RH, Pantoja JP, Sierra M, Herrera MF. Hypoparathyroidism After Total Thyroidectomy: Importance of the Intraoperative Management of the Parathyroid Glands. *World J Surg*. 2019;43(7):1728-1735.
6. Bai B, Chen Z, Chen W. Risk factors and outcomes of incidental parathyroidectomy in thyroidectomy: A systematic review and meta-analysis. *Plos One*. 2018;13(11):e0207088.
7. Karadeniz E, Akcay MN. Risk Factors of Incidental Parathyroidectomy and its Relationship with Hypocalcemia after Thyroidectomy: A Retrospective Study. *Cureus*. 2019;11(10):e5920.
8. Dedivitis RA, Aires FT, Cernea CR. Hypoparathyroidism after thyroidectomy: prevention, assessment and management. *Curr Opin Otolaryngol Head Neck Sur*. 2017;25(2):142-146.
9. Park I, Rhu J, Woo JW, Choi JH, Kim JS, Kim JH. Preserving parathyroid gland vasculature to reduce post thyroidectomy hypocalcaemia. *World J Surg*. 2016;40:1382-1389.
10. Kakava K, Tournis S, Papadakis G, Karelis I, Stampouloglou P, Kassi E, Triantafillopoulos I, Villiotou V, Karatzas T. Postsurgical hypoparathyroidism: a systematic review. *In Vivo*. 2016;30:171-179.
11. Puzziello A, Gervasi R, Orlando G, Innaro N, Vitale M, Sacco R. Hypocalcemia after total thyroidectomy: could intact parathyroid hormone be a predictive factor for transient postoperative hypocalcemia? *Surgery*. 2015;157:344-348.
12. Canu GL, Medas F, Longheu A, Boi F, Docimo G, Erdas E, Calo' PG. Correlation between iPTH Levels on the First postoperative Day After Total Thyroidectomy and Permanent Hypoparathyroidism: Our Experience. *Open Med (Wars)*. 2019;14:437-442.