

Review Article



Prevention, Identification and Management of Postoperative Hypoparathyroidism

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ABSTRACT

The objective of this article is to detail and present our experience on the incidence and management of parathyroid dysfunction after thyroid surgery. Selective evaluation of original articles and reviews that were retrieved by a PubMed search over the years 1990 to 2018, as well as of the recommendations of medical societies including the American, European and Asian Thyroid/Endocrine Associations. The literature presents several contributions, with controversial results. The recommended management for the diagnosis and treatment of parathyroid dysfunction after bilateral thyroid surgery or recurrent surgery consists of an intact parathyroid hormone (iPTH) determination 12–24 hours after surgery and calcium substitution in iPTH <15 pg/mL, no substitution with iPTH ≥15 pg/mL. This procedure is safe for the patient and is accepted by patients and social insurances (for short hospital stay).

Keywords: Thyroid gland; Thyroid disease; Parathyroid glands; Parathyroid hormone

PREFACE

Postoperative hypoparathyroidism is a frequent, if not diagnosed or late recognized clinically serious complication after bilateral thyroid surgery or recurrent surgery in addition to the paresis of the recurrent laryngeal nerve (RLN).

The definition of hypoparathyroidism varies widely in literature (1-5).

Based on current investigations, postoperative hypoparathyroidism after thyroid surgery is defined as an intact parathyroid hormone (iPTH) below 15 pg/mL with normal, low average or decreased serum calcium (Ca, protein corrected) (1).

It is a transient phenomenon when normalization of normal level of Ca level without continuing the Ca substitution happens within the first 6 months (2). Permanent parathyroid

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

gland dysfunction occurs when no iPTH normalization, continuation of Ca substitution proceeds 6 months postoperatively (2).

If this strict definition is used, it is found to have a transient hypoparathyroidism in 21%–50% after thyroidectomy and 1% to 10% permanent prevalence.

Most patients with hypocalcemia after total thyroidectomy will recover the parathyroid function in a few weeks, but some 20%–30% of them will still be in the need for replacement therapy one month after surgery and about 5%–10% of those will develop permanent hypoparathyroidism (3).

Many efforts are required to address the problem of a consensus for best define this complication. But there are inconsistent definition, different parameters and parameter combinations currently used for hypoparathyroidism (3-5). As a obvious consequence, a wide range of reported incidences of transient and permanent postoperative hypoparathyroidism are presented in literature (1-5).

Effective treatment of hypoparathyroidism requires consistent serial determinations. The information about low iPTH concentration allows to start the proper and timely pharmacotherapy and avoid clinical manifestation of hypocalcaemia.

Acute hypocalcemia may lead to syncope, congestive heart failure, and angina due to the multiple cardiovascular effects (5). Neuromuscular and neurologic symptoms may also occur as numbness and tingling sensations in the perioral area or in the fingers and toes, muscle cramps, particularly in the back and lower extremities; may progress to carpedal spasm (i.e., tetany), wheezing; may develop from dysphagia, bronchospasm. Laryngospasm is feared complication in a patient who already has an associated RLN paralysis (5).

GENESIS

Although postoperative hypocalcemia has been related to several demographic and metabolic causes, iPTH decline, resulting from inadvertent excision or devascularization of the parathyroid glands, are the most common causes (6).

There are surgical techniques described to help preserve the inferior and superior parathyroid gland in situ during thyroidectomy (**Fig. 1**). Applying the proper surgical concepts improves the rate of inferior and superior parathyroid gland preservation in situ and decreases the incidence of transient postoperative hypoparathyroidism (6).

A sound knowledge of regional anatomy combined with a meticulous operative technique are essential to avoid injury to these structures (**Fig. 2**).

Intraoperative causes of postoperative hypoparathyroidism include manipulation, misdirected blood flow, unrecognized parathyroid devascularization as part of thyroid dissection and unrecognized (accidental) removal of one or more parathyroid glands (7-10).

Not insignificantly, the microvasculature of the parathyroid glands is burdened by the long-term/difficult identification of the RLNs (6). Early and definitive identification of the RLN with intraoperative monitoring (IONM) may minimize parathyroid glands trauma.

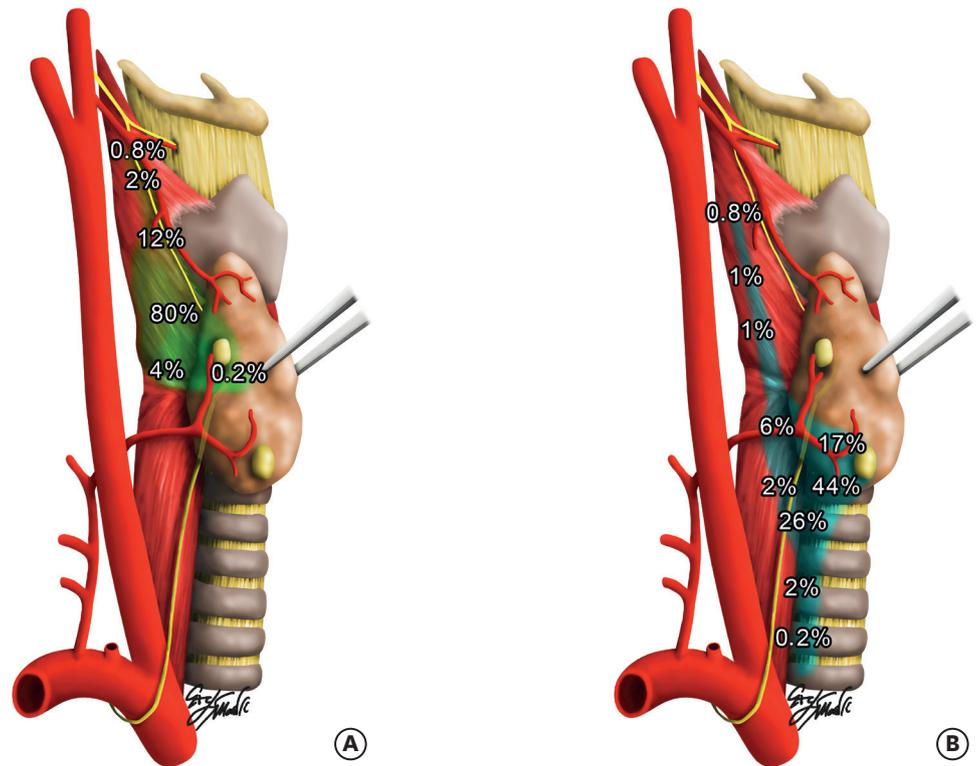


Fig. 1. The terms “superior” and “inferior” refer to a gland’s embryologic origin. (A) The superior parathyroid glands are usually one to 2 centimeters cranial to the junction of the RLN with the inferior thyroid artery and within 1 cm of the entry point for the RLN into the ligament of Berry and the cricoid cartilage. Superior parathyroid glands can be undescended, or can be parapharyngeal, retropharyngeal, or retrotracheal within the middle cervical/mediastinal compartment. (B) The 2 inferior parathyroid glands reside in the anterior mediastinal compartment, anterior to the RLN. They are most often found in the thyrothymic tract, or just inside the thyroid capsule on the inferior portion of the thyroid lobes. The parathyroid glands are variable in number: 3 or more small glands. Occasionally, some individuals may have 6, 8, or even more parathyroid glands. RLN = recurrent laryngeal nerve.

Postoperatively, compression by a local hematoma may be another cause (7-10).

Postoperative hypocalcaemia due to dysfunction of the parathyroid glands (inferior) is the most common complication after total thyroidectomy plus central neck dissection (CND) (10). This is a very important issue due to the increased frequency of central compartment dissections in last years (10-20).

The number of parathyroid glands remaining in situ is a key variable to understand the pathogenesis of protracted hypoparathyroidism and the chances for restoration of the parathyroid function. Thus, targeted identification (if possible of all parathyroid glands) and atraumatic, capsule-dissection of the glands can reduce postoperative dysfunctions. It is important to respect the venous drainage.

The exact knowledge of anatomy and its variation in position and number is indispensable (11,12).

An indispensable technical aid for better identification, more accurate preparation and better assessment of the perfusion of the parathyroid glands are the magnifying glasses (2.5 to 3.5-fold magnification) in open surgery and the high definition (HD) cameras in endoscopic/robotic procedures (**Fig. 3**) (13).

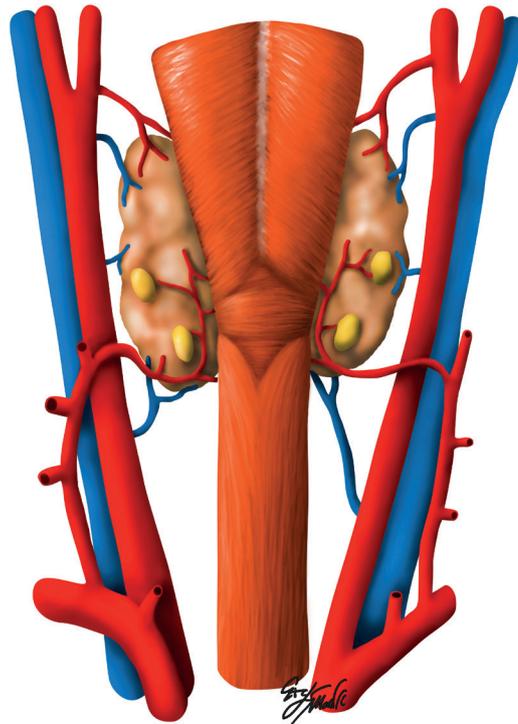


Fig. 2. The superior parathyroid glands receive their blood and drainage from the inferior thyroid vessels in more than 90% of cases, rarely from the superior ones. The inferior parathyroid glands receive a variable blood supply, from either the ascending branch of the inferior thyroid arteries or the thyroid ima artery. The inferior thyroid artery arises from the subclavian arteries. Each parathyroid vein drains into the superior, middle and inferior thyroid veins. The superior and middle thyroid veins drain into the internal jugular vein, and the inferior thyroid vein drains into the brachiocephalic vein.

The critical use of currently used vessel sealing devices, bipolar coagulation and/or ultrasonic accessories, seems to reduce peri- and postoperative circulatory disturbances (14,15). However, there are no prospective, randomized studies that support this subjective impression.

If the perfusion of a parathyroid gland cannot be reliably preserved during the preparation, it should be autografted into a muscle pouch of the sternocleidomastoid muscle (according to previous histological confirmation of the gland) (16). The “prophylactic en-principe autotransplantation” of a parathyroid gland during thyroidectomy did not yield any advantages (17).

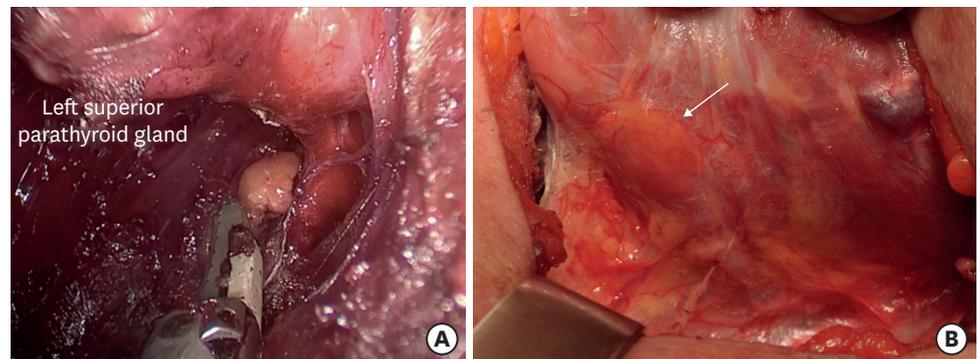


Fig. 3. Identification and preservation of parathyroid gland. (A) Transoral endoscopic thyroidectomy vestibular approach. (B) Open conventional thyroidectomy.

Table 1. Frequency of parathyroid gland autographs, temporary and permanent hypothyroidism after thyroidectomy with and without CND, level 6 and 7

Thyroidectomy	No.	Gland autographs	Temporary hypoparathyroidism	Permanent hypoparathyroidism
Without CND	298	15 (5)	56 (18.7)	3 (1)
Unilateral CND	21	2 (9.5)	5 (23)	0 (0)
Bilateral CND	100	7 (7)	22 (22)	2 (2)
Total	419	24 (5.7)	83 (19.8)	5 (1.1)

Values are presented as number (%). No statistical significance differences are found when comparing between groups ($P > 0.05$). CND = central neck dissection.

It is the important principle that every parathyroid glands should be treated as if it were the last remaining one.

A recent study introduce the ‘*TBP layer*’ (thymus, blood vessel, inferior parathyroid gland layer) concept for preserving the inferior parathyroid gland in situ during CND, and to evaluate its effectiveness (21). The study group included patients with primary papillary thyroid cancer who underwent total thyroidectomy with CND using the new surgical concept (21). The control group included sex- and age-matched patients. The proportion of inferior parathyroid glands preserved in situ and postoperative hypoparathyroidism rates in the 2 groups were compared. There were 181 patients in the study group and 306 in the control group (21). There were no significant differences between the groups in tumor size, multifocality, extrathyroidal extension, and number of harvested and metastatic central lymph nodes. The rate of inferior parathyroid gland preservation in situ was significantly improved from 37.9 to 76.3 per cent on the left side ($P < 0.001$), and from 52.0 to 77.9 per cent on the right side ($P < 0.001$), in the study group compared with the control group. The incidence of transient hypoparathyroidism decreased significantly from 35.0 to 7.2 per cent ($P < 0.001$) (21).

The view that gland autograph, parathyroid dysfunction significantly increases with the extent of the surgical intervention (subtotal resection vs. thyroidectomy, CND yes vs. no) is not confirmed from a review from our experience, summarized in **Table 1**.

INDOCYANINE GREEN (ICG)

It is worth nothing that identification of parathyroid glands does not equal safe preservation, as some studies demonstrated that it is not the number of parathyroid glands identified, but the number of parathyroid glands preserved in situ that matters. Therefore, a non-invasive objective and reliable way to localize parathyroid glands and assess their viability intra-operatively is warranted. In this aspect, modern technology such as the ICG as near-infrared fluorescent dye for real-time in situ parathyroid glands perfusion monitoring may have a potential role (**Fig. 4**).

ICG angiography reliably predicts the vascularization of the parathyroid glands and obviates the need for postoperative measurement of Ca and PTH, and supplementation with Ca in patients with at least one well perfused parathyroid gland (22).

A randomized controlled trial was undertaken to determine whether intraoperative parathyroid gland angiography with ICG could predict postoperative hypoparathyroidism, and obviate the need for systematic blood tests and oral Ca supplementation.

Between September 2014 and February 2016, patients who had at least one well perfused parathyroid gland on ICG angiography were randomized to receive standard follow-up

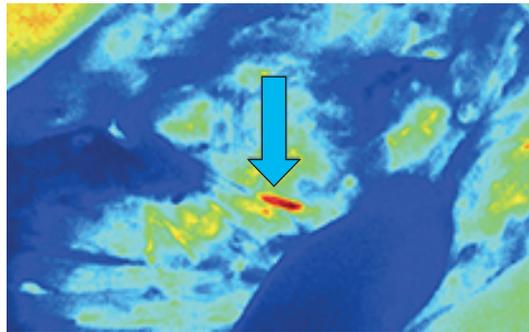


Fig. 4. ICG as near-infrared fluorescent dye for real-time in situ parathyroid glands perfusion monitoring. ICG = indocyanine green.

(measurement of Ca and PTH on postoperative day (POD) 1 and systematic supplementation with Ca and vitamin D; control group) or no supplementation and no blood test on POD 1 (intervention group) (22). In all patients, Ca and PTH levels were measured 10–15 days after thyroidectomy. The primary endpoint was hypocalcaemia on POD 10–15. A total of 196 patients underwent ICG angiography during thyroid surgery, of whom 146 had at least one well perfused parathyroid gland on ICG angiography and were randomized. None of these patients presented with hypoparathyroidism, including those who did not receive Ca supplementation (22). The intervention group was statistically non-inferior to the control group (exact 95% confidence interval [CI] of the difference in proportion of patients with hypocalcaemia -0.053 to 0.053 ; $P=0.012$). Eleven of the 50 excluded patients, in whom no well perfused parathyroid gland could be identified by angiography, presented with hypoparathyroidism on POD 1, and six on POD 10–15, which was significantly different from the findings in randomized patients ($P=0.007$) (22).

PARATHYROID HORMONE (PTH) AND CA LEVELS

Traditionally, sequential measurement of Ca levels is recommended after bilateral thyroid interventions, at least on the first 2 to 3 PODs (1). In contrast to the very good prediction of the parathyroid function on the basis of the iPTH level, the Ca as “success parameter” alone on the first POD hardly correlates with the prognosis regarding the development of postoperative hypoparathyroidism (1,2).

Table 2 summarize our experience on PTH and Ca levels determination on the 1st POD after 298 bilateral thyroidectomy. Ca levels in the first POD is not predictive, iPTH instead significantly anticipates parathyroid function (**Table 2**). Only the course of the Ca level on other days allows the reliable detection of parathyroid dysfunction, but is neither

Table 2. PTH and Ca levels on the 1st postoperative day after bilateral thyroidectomy

iPTH (pg/mL)	No. (%)	Serum Ca (mmol/L)		
		<1.8	1.8–2.0	>2.0
>15	233 (78)	1 (0.3)	11 (3.6)	221 (74)
10–15	44 (14)	2 (0.6)	19 (6.3)	23 (7)
<10	21 (7)	4 (1.3)	16 (5.3)	1 (0.3)
Total	298	7 (2.3)	46 (15.4)	245 (82)

Values are presented as number (%). Normal range: serum Ca: 2.0–2.6 mmol/L, iPTH: 15–65 pg/mL. Central lymph node dissection cases are excluded from the analysis.

PTH= parathyroid hormone; Ca = calcium; iPTH = intact parathyroid hormone.

comfortable for the patient (multiple blood samples) nor for the social cost (prolonged hospitalization) (1).

Intraoperative iPTH monitoring (IOPTH) with documentation of adequate decrease of elevated iPTH levels to predict (targeted) normocalcemia is established in primary hyperparathyroid surgery (23). IOPTH was also recommended as part of radical thyroid surgery to assess the function of the normal in situ remaining parathyroid glands (23). This method is costly because at least 3 iPTH determinations are required to document intraoperative iPTH history and additional medical technical assistance must be provided. Also, iPTH accessory meters are not always available, especially in smaller surgical departments hospitals (23).

Prospective randomized trial of prophylactic parathyroid autografting after thyroidectomy vs. iPTH levels have shown that patients with an iPTH level <10 pg/mL (and only on this condition) are subject to parathyroid autografting “by principle” compared to patients with “on-demand” parathyroid autotransplantation (subjective criteria) will benefit (but no for permanent hyperparathyroidism in this patient group) (24). However, an iPTH level cannot be used until 10–20 minutes after the end of the operation to decide whether parathyroid autotransplantation is necessary (24).

The iPTH level 4 hours postoperatively is the most meaningful (24-26). More detailed studies on the validity of iPTH measurements at the end of the operation compared to later measurements showed that iPTH levels are best predictable at 4 hours postoperatively and later in actual parathyroid function (25,26). Thus, IOPTH and the measurement immediately after the end of the operation have less practical significance than originally hoped (24-26).

Although rare, postoperative life-threatening rebleeding occurs within the first 24 hours postoperatively (27-29). Concepts with inpatient short-term stays take into account these experiences and recommend at least 24 hours stationary observation (28). Therefore, the best time for the postoperative examination of the parathyroid metabolism is the one-time measurement of the iPTH level on the morning of the first POD (2).

In a prospective “standard protocol” it could be shown that a once-only measured iPTH level 12–24 hours postoperatively, independent of the serum Ca level, can predict the postoperative parathyroid function with a sensitivity and specificity of 99% (2).

Short-term and long-term observations have shown that patients with an iPTH level ≥ 15 pg/mL (normal value 15–65 pg/mL) have normal parathyroid metabolism, no Ca and/or vitamin D substitution need to be discharged and without further checks in home care (2).

CA AND VITAMIN D SUBSTITUTION

Table 3 describes Selberherr et al. (2,30) protocol for Ca/vitamin D substitution as a function of iPTH levels 12–24 hours postoperatively after bilateral thyroidectomy (with/without CND).

Patients with an iPTH level <10 pg/mL can be discharged without symptoms with an oral “standard substitution” consisting of Ca carbonate and cholecalciferol, standard dose (**Table 3**).

Table 3. Ca/vitamin D substitution as a function of iPTH levels 12–24 hours postoperatively and in the course of (almost total) thyroidectomy (with/without CND, level 6–7)

Variables	Laboratory (iPTH, [total Ca])		
12–24 hours postoperative			
iPTH (pg/mL)	>15	10–15	<10
Parathyroid function	Normal	Questionable normal hypofunction	Underactive
Substitution “standard dose”	None	Yes	Yes
Ca in mg/cholecalciferol in I.E. p.o.		2×1,000/880	3×1,000/880
Calcitriol in µg [1,25(OH)2D3]		2×0.25	3×0.25
Reduction 1 week postoperatively “maintenance dose”		No	Yes
Ca in mg/cholecalciferol in I.E. p.o.			2×1,000/880
Calcitriol in µg [1,25(OH)2D3]			2×0.25
Laboratory (iPTH) 2 weeks postoperatively		Yes	Yes
iPTH (pg/mL)		>15	<15
Substitution		Finish	Continue
Laboratory (iPTH) 6–8 weeks postoperatively			Yes
iPTH (pg/mL)			>15
Substitution			Finish

Modified from references 2 and 30.

Ca = calcium; iPTH = intact parathyroid hormone; CND = central neck dissection; I.E. = International Units; p.o. = per os.

The addition of calcitriol [1 α , 25 (OH) 2-cholecalciferol = 1 α , 25 (OH) 2 vitamin D3 or 1,25 (OH) 2D] improves intestinal Ca uptake (2).

According to the protocol, after 1 week the dosage is reduced by one third (“maintenance dose”) in order to prevent iatrogenic hypercalcaemia (2,30).

Ca or vitamin D doses must be closely monitored.

In a few patients, iPTH levels between 10 and 15 pg/mL are documented. The development of a normal or subfunction is not predictable. These patients may either be discharged with a “standard dosage” on the 1st POD or remain stationary for further laboratory control on the 2nd postoperative day. Parathyroid function has already been normalized in at least one third of patients (iPTH \geq 15 pg/mL) (2,30). Discharge is possible without substitution, while patients with an iPTH in the “gray area” must be substituted according to the standard protocol (Table 3).

Depending on the 14-day postoperatively measured iPTH level, substitution is maintained at the maintenance dose (iPTH <15 pg/mL) or when normalized (iPTH \geq 15 pg/mL) (Table 3).

CONCLUSION

Many thyroidectomies are performed by unexperienced surgeons. We believe that incidence of permanent hypoparathyroidism is underestimated. Endocrine surgeons are to perform functionally safe thyroidectomy and reduce the surgical complications related to parathyroid injury (30). And to do so, the best surgical tips for parathyroid preservation is to take time, keep trying, never give-up, and do the surgeon's best, despite the low success rate of parathyroid preservation in the beginning of thyroid surgery. Surgeons should try to identify and preserve both the inferior and superior parathyroid glands, preserve the vascular supply and venous drainage of the glands (31).

There is no formulaic technique for parathyroid preservation. However, to improve such surgical skill, the surgeons must learn about the actual anatomy of the parathyroid glands,

focus on the micro-looking branches of parathyroid supplying vessels that originate from the main vessel trunk, and explore every possible location that might bear the parathyroid glands (31). To increase the chance of preserving the final vessel branches that supply the parathyroid, one must not ligate the vessels at their origin. Instead, approach from the distal end of the branches and forward proximally. The surgeon must clearly see the pulse of the peripheral vessel branches originating from either superior thyroidal artery or inferior thyroidal artery that supply the preserved parathyroid gland with no color change at the end of the procedure (31).

The presented management records the parathyroid gland function safely by an iPTH measurement 12–24 hours postoperatively. In contrast to IOPTH, the recommended procedure immediately and postoperatively considers unpredictable functional impairments of the parathyroid glands by (clinically irrelevant) hematomas and/or swellings. The one-off evaluation of postoperative parathyroid metabolism with an iPTH measurement is cost-effective at 17.60 EUR per determination (2). Inpatient short-term stay further reduces inpatient treatment costs (2,30).

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