

## Research Article

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# Correlation between iPTH levels on the first postoperative day after total thyroidectomy and permanent hypoparathyroidism: our experience

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**Abstract:** Permanent hypoparathyroidism is the most common long-term complication after thyroidectomy. We evaluated whether iPTH concentrations on the first postoperative day may be a good predictor of this complication.

Patients undergoing thyroidectomy in our Unit between January 2017 and February 2018 who developed postsurgical hypoparathyroidism were analysed. According to iPTH values on the first postoperative day and on the basis of the detection threshold of the iPTH test used, patients were divided into 2 groups: Group A (iPTH < 6.3 pg/mL, undetectable), Group B (iPTH ≥ 6.3 pg/mL).

Seventy-five patients were included in this study: 64 in Group A and 11 in Group B. Permanent hypoparathyroidism occurred in 14 (21.88%) patients in Group A, while none developed this complication in Group B. When iPTH was < 6.3 pg/mL, the sensitivity for the prediction of permanent hypoparathyroidism was 100%, the specificity was 18.03%, the positive predictive value was 21.88% and the negative predictive value was 100%.

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No patient with iPTH ≥ 6.3 pg/mL on the first postoperative day developed permanent hypoparathyroidism. On the other hand, iPTH concentrations < 6.3 pg/mL have not proved to be a strong predictor of this condition. However, this cut-off value can be useful to identify patients at risk of developing this complication.

**Keywords:** Permanent hypoparathyroidism; Total thyroidectomy; Intact parathyroid hormone; Undetectable iPTH

## 1 Introduction

Total thyroidectomy (TT) is the most widely surgical procedure performed in endocrine surgery, for both benign and malignant thyroid diseases.

Hypoparathyroidism (HPP) is a common complication after TT [1-9]. This condition is characterized by decreased values of circulating parathyroid hormone leading to hypocalcemia and slightly higher phosphate levels.

Hypocalcemia can cause symptoms ranging from numbness of the face and hands to tetany, convulsions and suffocation (caused by laryngeal and diaphragmatic spasms). Moreover, manifestations of chronic hypocalcemia include some severe conditions, such as nephrocalcinosis, kidney stones, chronic kidney disease, myocardial dysfunction, basal ganglia calcifications, cataracts and dental abnormalities [10-15].

In case of HPP, the main purpose of treatment is to maintain normal blood calcium levels. Medical therapy of hypocalcemia consists in the administration of calcium and vitamin D [16].

Although HPP after TT reverses spontaneously within a few months in most cases, in a few patients, it can persist for more than 1 year [4]. In this case this condition has to be considered permanent and, to avoid the subtle but potentially lethal complications of chronic hypocalce-

mia, long-term therapy and careful follow-up are mandatory. However, long-term calcium supplementation can also cause side effects, such as gastrointestinal reactions, myocardial infarction and urinary calculi [17].

The incidence of transient and permanent hypoparathyroidism is 6.9–46% and 0–10% respectively [2, 5, 18].

Costs to society in terms of increased postoperative stay, sick leave, medical treatments and surveillance, with periodic laboratory testing, are considerable. Moreover, permanent HPP is an important cause of medical litigation.

Currently, there are no reliable immediate postoperative biochemical parameters which allow the identification of those patients with postsurgical HPP who will develop permanent HPP [19]. In order to ensure patients the best follow-up, it would be very useful to be able to predict the risk of permanent HPP at an early stage after surgery. To date, there is still no consensus about the correlation between postoperative intact parathyroid hormone (iPTH) values and the development of this condition [20–34]. The aim of the present study was to investigate this topic. In particular, we evaluated whether iPTH concentrations on the first postoperative may be a good predictor of permanent HPP.

## 2 Methods

This is a retrospective study on patients who underwent thyroidectomy in our Unit of General and Endocrine Surgery (University of Cagliari) between January 2017 and February 2018.

Only patients with postsurgical HPP after TT were considered. Among these, those simultaneously submitted to lateral and/or central neck dissection were included in this study, while those who simultaneously underwent parathyroidectomy or parathyroid autotransplantation were excluded.

All operations were performed under general anaesthesia. Lateral and/or central neck dissection was performed in patients with preoperative or intraoperative suspicion of lymph node metastases. Recurrent laryngeal nerves and parathyroid glands were systematically searched and identified. Intraoperative nerve monitoring (IONM) was routinely used in order to facilitate nerve identification and to confirm its functional integrity. Haemostasis was mainly achieved by means of energy-based devices. One or two closed suction drains were placed below the strap muscles and removed when the secretion volume was less than 20 ml over 24 hours. The cervical

linea alba and platysma were sutured with absorbable sutures and skin was closed by a continuous intradermal suture.

Demographic data (sex, age), information on surgical procedure (extent of surgery) and histopathological findings were recorded.

Serum calcium and iPTH levels were assayed preoperatively and on the first and second postoperative days. Postsurgical HPP was defined as iPTH < 10 pg/mL on the second postoperative day (normal range = 10–65 pg/mL). All patients with postsurgical HPP, even if asymptomatic, received treatment with calcium carbonate (1–3 g/day) and calcitriol (0.5–1.5 µg/day). In case of severe hypocalcemia, intravenous calcium gluconate was used.

According to iPTH values on the first postoperative day and on the basis of the detection threshold of the iPTH test used, patients were divided into 2 groups: those with iPTH < 6.3 pg/mL (undetectable) were included in Group A, those with iPTH ≥ 6.3 pg/mL in Group B.

Permanent HPP was defined as iPTH concentrations below the normal range for more than 12 months.

Intact parathyroid hormone was measured with ADVIA Centaur® XPT Immunoassay Systems (Siemens Healthcare Diagnostics, Inc.).

Statistical analyses were performed with MedCalc® 18.0.2. Fisher exact test was used for categorical variables and t-test for continuous variables. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. *P* values < 0.05 were considered statistically significant.

**Ethical approval:** The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

**Informed consent:** Informed consent has been obtained from all individuals included in this study.

## 3 Results

A total of 75 patients were included in this study. There were 16 (21.33%) males and 59 (78.67%) females, with a mean age of 49.25 ± 16.77 years old. Sixty-six (88%) patients underwent total thyroidectomy, 4 (5.33%) total thyroidectomy with ipsilateral central neck dissection, 3 (4%) total thyroidectomy with central neck dissection

**Table 1:** Demographic data, information on surgical procedure and histopathological findings.

	Total (n = 75)	Group A (n = 64)	Group B (n = 11)	P value
Sex				
- Male	16 (21.33%)	15 (23.44%)	1 (9.09%)	NS
- Female	59 (78.67%)	49 (76.56%)	10 (99.91%)	
Age (mean ± SD)	49.25 ± 16.77	47.91 ± 16.99	57.09 ± 13.55	NS
Extent of surgery				
- TT	66 (88%)	56 (87.50%)	10 (90.91%)	NS
- TT + ICND	4 (5.33%)	3 (4.69%)	1 (9.09%)	NS
- TT + CND	3 (4%)	3 (4.69%)	0	NS
- TT + CND + LND	2 (2.67%)	2 (3.12%)	0	NS
Thyroid weight (mean ± SD)	58.44 ± 61.08	59.14 ± 63.79	54.36 ± 44.11	NS
Histological diagnosis				
- Benign disease	43 (57.33%)	36 (56.25%)	7 (63.64%)	NS
- Malignancy	32 (42.67%)	28 (43.75%)	4 (36.36%)	

TT, total thyroidectomy; ICND, ipsilateral central neck dissection; CND, central neck dissection; LND, lateral neck dissection

**Table 2:** Patients who developed permanent HPP.

	Total (n = 75)	Group A (n = 64)	Group B (n = 11)	P value
Permanent hypoparathyroidism	14 (18.67%)	14 (21.88%)	0	NS

and 2 (2.67%) total thyroidectomy with central and lateral neck dissection. Mean thyroid weight was 58.44 ± 61.08 g. Histopathological diagnosis was benign disease in 43 (57.33%) patients and malignancy in 32 (42.67%).

Of the 75 patients, 64 were included in Group A and 11 in Group B.

In Group A, there were 15 (23.44%) males and 49 (76.56%) females, with a mean age of 47.91 ± 16.99 years old. Fifty-six (87.50%) patients underwent total thyroidectomy, 3 (4.69%) total thyroidectomy with ipsilateral central neck dissection, 3 (4.69%) total thyroidectomy with central neck dissection and 2 (3.12%) total thyroidectomy with central and lateral neck dissection. Mean thyroid weight was 59.14 ± 63.79 g. Histopathological diagnosis was benign disease in 36 (56.25%) patients and malignancy in 28 (43.75%).

In Group B, there were 1 (9.09%) male and 10 (99.91%) females, with a mean age of 57.09 ± 13.55 years old. Ten (90.91%) patients underwent total thyroidectomy and 1 (9.09%) total thyroidectomy with ipsilateral central neck dissection. Mean thyroid weight was 54.36 ± 44.11 g. His-

**Table 3:** Correlation between iPTH levels < 6.3 pg/mL on the first postoperative day and the development of permanent HPP.

Sensitivity	100%
Specificity	18.03%
PPV	21.88%
NPV	100%

PPV, positive predictive value; NPV, negative predictive value

topathological diagnosis was benign disease in 7 (63.64%) patients and malignancy in 4 (36.36%).

Demographic data, extent of surgery and histopathological findings were comparable between the 2 groups.

Permanent HPP occurred in 14 (21.88%) patients in Group A, while none developed this complication in Group B (this difference was not statistically significant).

When iPTH levels were < 6.3 pg/mL on the first postoperative day the sensitivity for the prediction of permanent HPP was 100%, the specificity was 18.03%, the PPV was 21.88% and the NPV was 100%.

## 4 Discussion

Despite progress in surgical technique and even in the most experienced hands, postsurgical HPP remains a challenging problem. Permanent HPP is the most common long-term complication after TT [1-9].

During surgery parathyroid glands can be damaged due to various mechanisms: thermal or mechanical stress, vascular injury (interrupted blood flow or impaired venous efflux) and involuntary removal [7, 31, 35-37].

Some factors have been associated with an increased risk of developing postsurgical HPP, such as female gender, thyroid cancer, Graves' disease, autoimmune thyroiditis and central neck dissection [1, 31, 35-45].

To date, there is still no consensus about the usefulness of postoperative iPTH levels to predict permanent HPP [20-34]. We evaluated whether iPTH values on the first postoperative day may be a good predictor of this complication. In the literature, we found some similar studies.

Almquist M. *et al* [29] stated that iPTH levels measured on the first postoperative day are associated with the risk of permanent HPP. In their experience, of 10 patients with permanent HPP, 8 had iPTH < 6.6 pg/mL and 2 had iPTH between 6.6 and 15 pg/mL. However, among the patients with iPTH values < 6.6 pg/mL the rate of this complication was only 19.2%.

In the study of Julián M.T. *et al* [30], iPTH concentrations  $\leq$  5.8 pg/mL on postoperative day 1 had 100% sensitivity, 81.5% specificity and 30% positive predictive value for permanent HPP. Conversely, iPTH levels > 5.8 pg/mL were correlated with normal parathyroid function in the long term.

In the experience of Wang J.B. *et al* [31], iPTH concentrations < 7 pg/mL on postoperative day 1 had sensitivity and negative predictive value of 100% for permanent HPP, but poor specificity and positive predictive value (70.19% and 8.63% respectively).

Kim H. *et al* [32] stated that the safest cut-off value of iPTH on the first postoperative day for the prediction of permanent HPP is 9.65 pg/mL (70.9% sensitivity and 100% specificity). None of the patients with iPTH > 9.65 pg/mL developed this complication.

In the study of Wang W. *et al* [33], iPTH levels  $\leq$  3.14 pg/mL on postoperative day 1 had 100% sensitivity for the prediction of permanent HPP, 95% specificity, 66.67% positive predictive value and 100% negative predictive value. Therefore, these researchers stated that iPTH levels > 3.14 pg/mL are great in assessing the absence of this complication.

Calvo Espino P. *et al* [34] found that a cut-off value of iPTH on the first postoperative day of 5 pg/mL has 95% sensitivity, 77% specificity, 21.6% positive predictive value and 99.6% negative predictive value for the prediction of permanent HPP. Therefore, they stated that this iPTH level, because of its high negative predictive value, is a useful predictor of permanent HPP.

In our study, we included only patients with postsurgical HPP, diagnosed on the basis of iPTH concentrations on the second postoperative day. According to our experience and that of other researchers, we consider iPTH values on postoperative day 2, rather than on postoperative day 1, more accurate in assessing the true functional state of parathyroid glands after TT. Among the patients considered, iPTH levels on the first postoperative day have been analysed. When iPTH concentrations were < 6.3 pg/mL, the sensitivity and the negative predictive value for permanent HPP were high (both 100%), but the specificity and the positive predictive value were poor, 18.03% and 21.88% respectively. It is important to underline that no patient with iPTH values  $\geq$  6.3 pg/mL developed this complication. As already explained above, in our study, the cut-off value was established on the basis of the detection threshold of the iPTH test used. Among the 2 groups obtained in this way, no statistically significant difference was found in terms of demographic data, extent of surgery and histopathological findings.

In light of the results obtained by our and the other studies analysed, to date, a cut-off value of iPTH on the first postoperative day accurate enough for the prediction of permanent HPP has not yet been identified. Thus, further larger and possibly multicenter studies are needed to better investigate this topic.

## 5 Conclusions

No patient with iPTH levels  $\geq$  6.3 pg/mL on the first postoperative day after TT developed permanent HPP. On the other hand, iPTH concentrations < 6.3 pg/mL have not proved to be a strong predictor of this condition (PPV, 21.88%; specificity, 18.03%). However, this cut-off value can be useful to identify patients at risk of developing this complication (sensitivity, 100%), who require a careful follow-up.

**Conflict of interest:** Authors state no conflict of interest.

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