



ORIGINAL ARTICLE

Chronic hypoparathyroidism after thyroid surgery: Benefits of specialized and personalized care in a tertiary public hospital

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Abstract

Introduction: As the number of thyroid operations increases, the incidence of complications also increases, including transitory and definite hypoparathyroidism. Since each patient presents different and unpredictable symptoms, affecting several organs and systems, they need personalized care. Even when patients presented with low calcium blood levels, the previous results were considered acceptable, usually using oral prescriptions of calcium carbonate and calcitriol. We created in March 2017 a specialized outpatient treatment facility for those patients focused on generating experience and knowledge about hypoparathyroidism. **Objective:** To analyze the challenges and the impact of specialized care in diagnosis, treatment and in follow-up of patients with postoperative hypoparathyroidism, with potential to improve teaching and further research possibilities in the subject. **Methods:** 61 patients were studied: 55 women, age 18-55. A retrospective study was performed, considering specialized guidelines. We also analyzed blood levels of calcium, parathyroid hormone, vitamin D, and other minerals; kidney function; bone structure. **Results:** Some patients needed drug dose adjustments up to 66%. We were able to identify kidney structural and functional changes. We could share those experiences in a multidisciplinary way, contributing significantly to provide more experience to the medical residents. **Conclusion:** Specialized outpatient treatment is responsible for providing more efficient and safe treatment to the patients, and it is also important to enable further medical research.

Keywords: hypoparathyroidism; parathyroid hormone; postoperative care; postoperative complications; thyroidectomy.

Introduction

The increase in the diagnosis of thyroid nodules comes together with an increase in the number of thyroidectomies. There was also an increase in the absolute number of patients with complications resulting from total thyroidectomy, in which the most common is hypoparathyroidism¹⁻⁴, either transient or definitive. Hypoparathyroidism is defined as the presence of hypocalcemia, associated with a low level (or inappropriate for the

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Financial support: None.

Conflicts of interest: No conflicts of interest declared concerning the publication of this article.

Submitted: June 24, 2019.

Accepted: October 01, 2019.

The study was carried out at Serviço de Cirurgia de Cabeça e Pescoço, Faculdade de Medicina, Hospital das Clínicas, Universidade de São Paulo (HC-FMUSP), São Paulo, SP, Brasil.

Article presented at the XXVII Congresso Brasileiro de Cirurgia de Cabeça e Pescoço, in August 2019



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corresponding calcium level) of PTH, the hormone produced by parathyroid glands, with or without clinical symptoms⁵.

Since it affects each patient, system and organ in a different and unpredictable way, hypoparathyroidism is a complex disease with potentially serious risks to life. Among its clinical manifestations⁶ there are symptoms related to acute hypocalcemia, such as paresthesia and cramps, which may lead to tetany, cardiac arrhythmia, convulsive crisis and laryngospasm. Chronic hypoparathyroidism can cause hypercalciuria by decreasing the effect of PTH on calcium tubular resorption, urinary lithiasis and nephrocalcinosis, reduction of vitamin D hydroxylation and hydroelectrolytic changes with hyperphosphataemia. It reduces bone metabolism⁷, making bones hypodynamic and more susceptible to fractures, with changes in bone density, osteosclerosis and cortical thickening. Patients with chronic hypoparathyroidism may develop early cataract and keratoconjunctivitis⁸, calcification of basal ganglia, extrapyramidal symptoms, dystonias, cognitive loss⁹, dental alterations¹⁰, alopecia, ungual changes and changes in cardiac circulation and conduction¹¹.

Levothyroxine replacement and relapse care are a natural priority in thyroid cancer patients' follow-up. The treatment of hypoparathyroidism usually aims at controlling symptoms and concentrations of serum calcium, PTH and vitamin D, by making up calcium with or without calcitriol prescription. The doctor who is following up cancer, mistakenly accepts the persistence of symptoms and subnormal serum calcium concentrations as the possible results to be reached with the available resources. Hypoparathyroidism bothers surgeons particularly, facing a surgery complication, which is always unpleasant.

To offer accurate and personalized care to patients with chronic hypoparathyroidism, the Hypoparathyroidism Outpatient Clinic was inaugurated on March 23rd, 2017, which is an innovation in clinical practice.

The objective is to present the challenges in diagnosis, identification of symptoms and complications, adjusting prescribed replacements and evaluating the initial impact on the patients' quality of life following-up a specific outpatient clinic. Also, reporting the perspectives in assistance, research and teaching resulting from the creation of the hypoparathyroidism outpatient clinic at the *Hospital das Clínicas of Faculdade de Medicina at Universidade de São Paulo*.

Methods

The sample included all patients enrolled in the hypoparathyroidism outpatient clinic of the *Hospital das Clínicas of Faculdade de Medicina at Universidade de São Paulo*, coded as 1CA8000. We evaluated the medical records of the 62 patients enrolled in the outpatient clinic, until the writing of this study, operated at our and other services. Of these, one was excluded due to inconsistency of data in the medical records, leaving 61 patients, 55 women and 6 men, aged between 18 and 81 years old, with an average of 53.4 years old. Forty-eight patients had undergone 3 outpatient appointments, four individuals were evaluated twice and nine patients underwent just one evaluation.

We evaluated retrospectively: age, sex, information on surgery, symptoms, dose of calcium carbonate and calcitriol, and levels of parathyroid hormone (PTH) and total calcium (CaT). Follow-up appointments are scheduled every six months.

Statistical analysis. The values obtained for each quantitative variable of parametric distribution were organized and described through mean and standard deviation. For qualitative ones were used absolute and relative frequencies. The comparison between the frequencies of dependent groups was performed by the McNemar test. The distributions were defined as parametric by the Kolmogorov-Smirnov test. For the comparison between the means of two dependent sample populations, we used the T-paired test and for more than two, we used the ANOVA test of repeated measurements with Bonferroni auxiliary test. The whole analyses used the statistical program SPSS® version 24.0 (SPSS® Inc; Illinois, USA) and all comparisons adopted a level of statistical significance of less than 5% ($p \leq 0.05$).

All patients were initially submitted to clinical evaluation. The usual serum dosages of calcium, phosphorus, parathyroid hormone, vitamin D, urea and creatinine were complemented by 24-hour calcium, phosphorus and creatinine dosage, ultrasound of kidneys and urinary pathways, bone mineral densitometry, with emphasis on forearm bones, contrast-free skull tomography, and chest X-ray. The process of ophthalmology evaluation for cataract research is ongoing but is not yet part of the care routine of these patients.

A careful protocol for patients with hypoparathyroidism was elaborated (Table 1).

Table 1. Care protocol.

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- QUARTERLY FOLLOW-UP APPOINTMENT (necessary for renewal of calcitriol dispensation - high-cost medicine)
 - EXAMS THAT SHOULD BE REQUESTED
 - INITIAL EVALUATION
 - PTH
 - PHOSPHORUS
 - 25 OH VIT D
 - CALCIURIA OF 24
 - CREATININE
 - URINARY TRACT USG
 - CONTRAST-FREE SKULL CT
 - OPHTHALMOLOGICAL EVALUATION
 - BONE DENSITOMETRY (SPINE, FEMUR, FOREARM)?
 - IN QUARTERLY RETURN (if they need calcitriol) OR SEMI-YEARLY (if they do not need):
 - TOTAL CALCIUM
 - PTH
 - PHOSPHORUS
 - 25 OH VIT D (only when replacement)
- Recommendation for oral administration:
Give priority for fractionation in meals rather than increasing doses
Creatinine Clearance
Men $(140 - \text{age}) \times \text{weight (kg)} / (\text{serum creatinine} \times 72)$
Women $[(140 - \text{age}) \times \text{weight (kg)} / (\text{serum creatinine} \times 72)] \times 0,85$
-

A model was also elaborated to record the appointments (Table 2) with two spreadsheets, one to facilitate the fractional use of calcium carbonate and calcitriol and another to facilitate the evolutionary view of the examinations by the physicians responsible for the patient.

Table 2. Care model.

NAME RGHC DIAGNOSIS: SURGERY: Date (/ /) Procedure undergone: Where it was done: ANATOMOPATHOLOGICAL: APPOINTMENT DATE: MEDICATION:						
BREAKFAST	MORNING SNACK	LUNCH	AFTERNOON SNACK	DINNER	NIGHT SNACK	
CaCO ₃						
Calcitriol						
EVOLUTION:						
PHYSICAL EXAM:						
EXAMS						
DATE						
TSH						
T4L						
TG						
ATG						
CA I						
CA TOTAL						
PTH						
VITAMINE D						
URINARY CALCIUM /24H						
PHOSPHORUS						
MAGNESIUM						
CREATININE						
URINARY CREATININE /24H						
CALCITONIN						
CEA						
IMAGE (/ /):						
CONDUCT:						
Assistant physician responsible for care:						

Results

Perception of impact on learning and teaching

The process of creating the chronic hypoparathyroidism outpatient clinic was preceded by a review of care guidelines of patients with this disease and discussion of experience and behaviors adopted in the group of bone metabolism of endocrinology of the Hospital. This improvement naturally reflected in increased interest and learning by assistant physicians and residents.

Impact on assistance

Procedures related to hypoparathyroidism performed (previous surgery)

Total thyroidectomy was performed in 95.1% of patients and prior partial thyroidectomy in 4.9%. Central cervical emptying was performed 58% of the time. Figure 1 shows the extension of neck dissection.

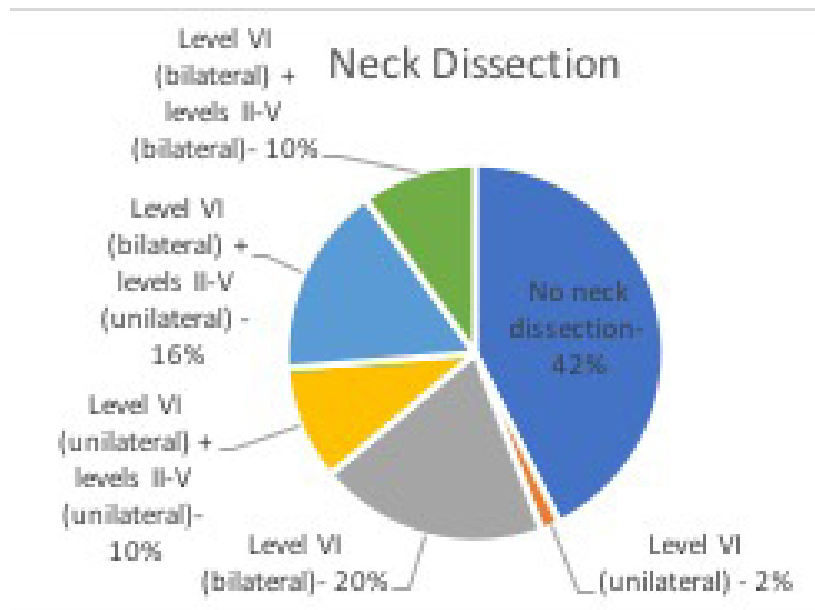


Figure 1. Extension of neck dissection.

The pathological diagnosis was papillary carcinoma in 45 patients and goiter in the other 16 (26.2%).

Prescribed changes in calcium carbonate and calcitriol carbonate dosages

Calcium and/or calcitriol dosages were modified in 32 individuals (66.7%). Among the 48 patients with two or more follow-up appointments, the prescribed dosage of calcium carbonate was reduced in 13 (27.1%), maintained in 16 (33.3%) and increased in 19 (39.5%). Calcitriol dosage was reduced in 13 patients (27.1%), maintained in 23 (47.9%) increased in 12 (25%), according to Table 3.

Table 3. Medications change in appointments of the chronic hypoparathyroidism outpatient clinic (n=48).

	Maintained	Increased	Reduced
Calcium carbonate	16 (33.3%)	19 (39.6%)	13 (27.1%)
Calcitriol	23 (47.9%)	12 (25%)	13 (27.1%)

Variations in the average dosages of calcium carbonate and calcitriol prescribed

The average use of CaCO₃ at the first appointment was 2,286mg/day, evolving to 2,567mg/day at the second appointment and 2,677mg/day at the third consultation.

Yet the average of calcitriol use was of 0.66mcg/day, evolving to 0.77mcg/day at the second appointment and 0.65mch/day at the third one. The comparison among the groups did not present difference in the average of medication use among the outpatient clinic appointments (ANOVA of repetitive measures).

Evolution of total calcium and PTH concentrations

PTH and total calcium (CaT) levels were measured and the values recorded in the first outpatient appointment were compared with the last examination performed. On average, PTH rose from 10.6 to 11.8pg/mL and CaT rose from 8.41 to 8.44mg/dL, without statistical significance to the T-paired test (PTH: p = 0.125; / CaT: p = 0.77).

Evolution of symptoms

One or more symptoms (paresthesia, cramp, sweating, abdominal colic and muscle tonic contractions) were present at the first appointment in 26 (42.6%) patients, and in 16 (33.4%) in the last evaluation (Table 4).

Table 4. Evaluation of symptoms in appointments of the chronic hypoparathyroidism outpatient clinic.

	First Appointment	Second Appointment	Third Appointment
Presence of symptoms	26 (42.6%)	26 (50%)	16 (33.4%)
Absence of symptoms	35 (57.4%)	26 (50%)	32 (66.6%)

Other findings

Some patients showed hypercalciuria, however, it was not possible to tabulate the data due to information inconsistency, despite the detailed protocol. A patient operated in 2005, without kidney complaints, reported ultrasound nephrocalcinosis.

Discussion

The persistence of symptoms and alteration in the examinations of patients with hypoparathyroidism after thyroidectomy brought us the idea of creating a specialized outpatient clinic. According to our knowledge, it is a pioneering initiative in Brazil and in the world.

The accuracy and availability of calcium, parathyroid and vitamin D dosages increased the number of diagnoses of hypoparathyroidism that, in the recent past, used to be diagnosed only when symptoms were reported.

For example, around 400 thyroidectomies are performed annually at the *Hospital das Clínicas* of the *Faculdade de Medicina* at Universidade de São Paulo (HCFMUSP) and at the *Instituto do Câncer do Estado de São Paulo* (ICESP), 74% of these cases due to cancer. Considering the best indicators of definitive hypoparathyroidism incidence published, ranging from 1 to 4.2%^{1,2,12,13}, we would have 4 to 16 new cases per year only in our services, however, this figure may be even higher, considering the cases in which therapeutic neck dissection was also carried out.

We reviewed the guidelines for the care of American and Brazilian Endocrinology societies. We also used the experiences of the bone metabolism group of Endocrinology, Rheumatology and Nephrology at HCFMUSP.

The prevalence and similarity of symptoms, in addition to the signs and alterations in the tests, were more easily identified and resulted in changes in the treatment of 2/3 of patients, with mild but clear improvement in symptoms and calcium levels.

Most changes were simple, such as dosage, manner, time and fractionation of medicines. The variation observed in calcitriol and calcium carbonate doses on patient evaluations after follow-up in the outpatient clinic is a reflection of the complexity of hypoparathyroidism. We tried to verify whether coming into the outpatient clinic could decrease, overall, the required dose of these medications. Although we did not find a result with statistical significance, the great variation found may be the reflection of a follow-up still short (only 3 appointments), but with great potential for specialization and improvement, with the possibility of creating future strategies optimized to these patients' management. We did not find in the current literature any publication with a proposal similar to this study, in an attempt to obtain better functional results with the individualization of treatment and specification of an outpatient clinic only for this purpose.

Within the broad spectrum of symptoms resulting from hypoparathyroidism and, more directly, from hypocalcemia, those with less evident clinical manifestations were more easily identified and those that depended on specific tests and, mainly, changes with greater potential for complications were investigated in a broad and effective way. The findings of hypercalciuria and a case of nephrocalcinosis, which had not been perceived before, and which are associated with serious health and quality of life risks, were very relevant.

The data obtained raise the complexity of not only the clinical, laboratory and imaging findings of the patient with post-surgical hypoparathyroidism but

also of treatment, which has the potential to improve symptoms and quality of life when performed in a focused and personalized way. There is also a need to continue the investigation of such a complex profile of patients, with additional studies on epidemiological profile, risk factors, prognostic factors and long-term follow-up, in order to improve the clinical practice in care of patients with hypoparathyroidism.

In the face of the rapid expansion of complex and often expensive technological innovations, we identified an opportunity to improve care, teaching and research with simple, low-cost action.

We have achieved the expected benefits with the creation of the Hypoparathyroidism Outpatient Clinic, with accurate care and training of professionals with experience in this pathology management, offering support to care for interested services and generating a specialized center to create and disseminate knowledge.

Conclusion

The creation of the outpatient clinic specialized in the care of patients with hypoparathyroidism after thyroidectomy, provided greater efficiency and safety in treatment, besides generating experience for Head and Neck Surgeons and other specialists involved in these patients' follow-up.

We believe that, in addition to the systematized evaluation of the natural history of this disease, the next step is to evaluate formally the impact in both hypoparathyroidism and its complications on these patients' quality of life. This will allow us to evaluate, through decision models, the impact of current and future therapeutic strategies on the clinical management of these patients.

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