

Benedito Rodrigues da Silva Neto
(Organizador)

MEDICINA:



A ciência e a tecnologia em busca da cura

3


Atena
Editora
Ano 2021

Benedito Rodrigues da Silva Neto
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APRESENTAÇÃO

Ciência é uma palavra que vem do latim, “*scientia*”, que significa conhecimento. Basicamente, definimos ciência como todo conhecimento que é sistemático, que se baseia em um método organizado, que pode ser conquistado por meio de pesquisas. Já a tecnologia vem do grego, numa junção de “*tecno*” (técnica, ofício, arte) e “*logia*” (estudo). Deste modo, enquanto a ciência se refere ao conhecimento, a tecnologia se refere às habilidades, técnicas e processos usados para produzir resultados.

A produção científica baseada no esforço comum de docentes e pesquisadores da área da saúde tem sido capaz de abrir novas fronteiras do conhecimento, gerando valor e também qualidade de vida. A ciência nos permite analisar o mundo ao redor e ver além, um indivíduo nascido hoje num país desenvolvido tem perspectiva de vida de mais de 80 anos e, mesmo nos países mais menos desenvolvidos, a expectativa de vida, atualmente, é de mais de 50 anos. Portanto, a ciência e a tecnologia são os fatores chave para explicar a redução da mortalidade por várias doenças, como as infecciosas, o avanço nos processos de diagnóstico, testes rápidos e mais específicos como os moleculares baseados em DNA, possibilidades de tratamentos específicos com medicamentos mais eficazes, desenvolvimento de vacinas e o consequente aumento da longevidade dos seres humanos.

Ciência e tecnologia são dois fatores que, inegavelmente, estão presentes nas nossas rotinas e associados nos direcionam principalmente para a resolução de problemas relacionados à saúde da população. Com a pandemia do Coronavírus, os novos métodos e as possibilidades que até então ainda estavam armazenadas em laboratórios chegaram ao conhecimento da sociedade evidenciando a importância de investimentos na área e consequentemente as pessoas viram na prática a importância da ciência e da tecnologia para o bem estar da comunidade.

Partindo deste princípio, essa nova proposta literária construída inicialmente de quatro volumes, propõe oferecer ao leitor material de qualidade fundamentado na premissa que compõe o título da obra, isto é, a busca de mecanismos científicos e tecnológicos que conduzam o reestabelecimento da saúde nos indivíduos.

Finalmente destacamos que a disponibilização destes dados através de uma literatura, rigorosamente avaliada, fundamenta a importância de uma comunicação sólida e relevante na área da saúde, assim a obra “Medicina: A ciência e a tecnologia em busca da cura - volume 3” proporcionará ao leitor dados e conceitos fundamentados e desenvolvidos em diversas partes do território nacional de maneira concisa e didática.

Desejo uma ótima leitura a todos!


Benedito Rodrigues da Silva Neto

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PREVENTION OF HYPOPARATHYROIDISM WITH THE USE OF CALCIUM-RICH FOODS IN THE TOTAL THYROIDECTOMY PRE-OPERATIVE PERIOD

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ABSTRACT: **Background:** Transient hypocalcemia after total thyroidectomy (TT) is a common surgical complication. Authors used calcium supplements in different doses and periods, mainly after TT to try to avoid hypocalcemia. Indistinct use has been challenged due to complications. Currently, the risk of hypocalcemia was assessed by measuring parathormone (PTH) after TT; however, without a consensus on the best time and amount to consider. The objectives of this study were to evaluate the incidence of hypoparathyroidism with the use of calcium-rich foods in the pre-operative period of TT, followed by a measurement of PTH performed 12 hours after such procedure. **Methods:** A preliminary study with 31 patients earmarked for TT. Patients were divided into two groups: (A) without calcium-rich foods intake in the TT pre-operative period; and (B) with the intake of calcium-rich foods, in the TT pre-operative period. These foods composing different menus have been suggested, based on the need for daily calcium intake, according to the age group and nutritional data of the Dietary reference intake (DRI). Beginning of the use of these foods has been standardized as being seven days before surgery, due to the slower calcium intestinal absorption process. **Results:** Group B, when compared to A, showed a significant difference between PTH values, before and after surgery (p value <0.001). **Conclusions:** Calcium-rich foods

intake in the conditions reported may be associated with lower rates of hypoparathyroidism.

KEYWORDS: Calcium, Hypocalcemia, Hypoparathyroidism, Thyroidectomy.

RESUMO: INTRODUÇÃO: Hipocalcemia transitória após tireoidectomia total (TT) é uma complicação cirúrgica comum, o que faz com que vários autores usem suplemento de cálcio em diferentes doses e períodos para tentar evitar a hipocalcemia. Indistintamente o seu uso tem sido desafiante devido às complicações. Normalmente, o risco de hipocalcemia é quantificado pela medida do paratormônio (PTH) após a TT, entretanto sem um consenso em que tempo e a quantidade a considerar; **OBJETIVOS:** Avaliar a incidência de hipoparatiroidismo com o uso de alimentos ricos em cálcio no período pré-operatório da TT, seguido pela medida do PTH após 12 horas do procedimento; **MÉTODOS:** Um estudo preliminar com 31 pacientes submetidos a TT, sendo os pacientes divididos em 2 grupos: (A) - sem a ingestão de alimentos ricos em cálcio no pré-operatório; (B) - com ingestão de alimentos ricos em cálcio no pré-operatório. Foram sugeridas diferentes refeições, baseado na necessidade da ingestão diária de cálcio, de acordo com a faixa etária e os dados nutricionais avaliados pela Ingestão referida de dieta (DRI). Foi padronizada o uso desses alimentos sete dias antes da cirurgia, devido ao processo da menor absorção de cálcio intestinal; **RESULTADOS:** Grupo B, quando comparado ao A, demonstrou uma diferença significativa entre os valores do PTH antes e após a cirurgia. ($p < 0,001$); **CONCLUSÕES:** A ingestão de alimentos ricos em cálcio nas condições assinaladas podem estar associada com menor taxa de hipoparatiroidismo.

PALAVRAS-CHAVE: Cálcio, hipocalcemia, hipoparatiroidismo, tireoidectomia.

INTRODUCTION

Despite all medical advances, total thyroidectomy surgeries are still accountable for hypocalcemia conditions, mostly transient (up to six months after surgery) and with quite variable rates as shown in the literature (0.3 to 80%).¹⁻⁴ Even in modern surgeries performed with a robot, authors have reported the occurrence of hypocalcemia. A local study involving 48 patients reports that three of them evolved with the referred condition (6.2%).⁵

Studies have associated hypoparathyroidism with the manipulation of the parathyroid glands, their systematic perquisition with a potential aggravation of their blood supply, the inadvertent removal of one or more glands, the operation of an inexperienced or experienced surgeon, hemodilution, large-volume and/or diving goiter, advanced thyroid cancer, hyperthyroidism, total thyroidectomy.^{2,3,6-10}

Calcium supplementation in the TT postoperative period is common practice and studies show that there is no consensus on the time and amount to be used. In fact, there is a variation from 1 to 21 days and from 600 to 7500 mg/day respectively.¹¹⁻¹⁶

Currently, calcium supplementation after thyroidectomy surgery is considered unnecessary in most patients, which may mask the real frequency of hypoparathyroidism and that this practice increases the risk of: hypercalcemia, kidney stones, constipation and absorption of nutrients such as iron and zinc from food.^{6,17,18}

Diagnosis of hypocalcemia begins to change with the use of intact PTH molecule

(i-PTH) in parathyroidectomy surgeries in 1991 and shortly thereafter in thyroidectomy surgeries where the slump in measured PTH values was observed to occur earlier than calcemia. It would be like a comparison of a few minutes versus 48 hours after the procedure.^{19,20}

The indication regarding the best time after surgery to perform the PTH dosing is not available in the literature, as well as the value to be considered as being suggestive of hypoparathyroidism. Different papers show a variation from 10 min to 24 hours and values between 6 and 19 pg/ml respectively.^{4,11,21,22}

A PTH value ≥ 15 pg/ml would be related to a low risk of the patient presenting symptoms of hypocalcemia and being safely discharged from the hospital on the first postoperative day and without the need for early oral calcium replacement.^{2,6,23}

Objectives

The main objective of this study was to evaluate the feasibility of using calcium-rich foods in the preoperative period of total thyroidectomies, associated with the dosage of PTH < 15 pg/ml, 12 hours after surgery to identify patients who may develop hypoparathyroidism (laboratory).

On the other hand the secondary objectives were: (a) to assess the incidence of transient hypoparathyroidism; (b) to identify patients who can safely be discharged from the hospital on the first postoperative day; (c) to recognize the subjects who will not require supplemental calcium; and (d) to establish a routine of conduct before and after total thyroidectomies.

METHODS

A preliminary study was carried out with 31 patients earmarked for total thyroidectomy at the teaching hospital PUCC, Sao Paulo, Brazil, between November 2017 and February 2019. The sample profile has been depicted in detail in Table 1.

| Sample profiles | Values |
|------------------------------|--------|
| Total patients | 31 |
| Gender (female: male) | 29:2 |
| Age (years) | 19-74 |
| Median age (years) | 49 |
| Diagnosis | |
| Malignant tumor | 10 |
| Benign tumor | 21 |
| Surgical procedures | |
| Total thyroidectomy (TT) | 29 |
| TT with cervical emptying | 02 |

Table 1: Sample profile.

The study was conducted with the approval of the PUC Research Ethics Committee (CEP).

All patients were informed about the investigation and the procedure to which they would be submitted through the Free and informed consent form (FICF), previously approved by the PUC-Campinas CEP.

Routine preoperative exams included: blood measurements (blood count, sodium, blood glucose, potassium, creatinine, urea and coagulogram), chest X- rays, electrocardiogram and pre-anesthetic evaluation. Previous dosages of thyroid hormones (TSH and free T4), ionic calcium and PTH were also performed.

Inclusion criteria

Patients with indication for total thyroidectomy due to benign disease (goiter with compressive or dipping symptoms, toxic and nontoxic multinodular goiter), suspected malignancy or confirmed malignant pathology through fine needle aspiration biopsy (FNAB) were included.

Exclusion criteria

Patients who were already using supplemental calcium, without clinical conditions for surgery; who did not agree to participate in the study; with laboratory alterations of calcium or PTH suggesting primary hyperparathyroidism, preoperative hypocalcemia; patients without all biochemical dosages; and those who did not adhere to the recommended calcium-rich feeding plan were excluded.

Before surgery, patients were randomly divided into two treatment groups. Group A: composed of 18 patients undergoing total thyroidectomy without instruction to ingest calcium-rich foods preoperatively; and group B: composed of 13 patients undergoing total thyroidectomy, with guidance to start eating calcium-rich foods seven days before surgery.

Foods rich in calcium were suggested in specific menus developed by the investigators in this study (Table 2) according to the DRI, which assesses the need for calcium intake, according to the age group.

| Example no. | Type of meal | Food | Calcium quantity (mg) | Total mg/day |
|-------------|--------------|--------------------------------------|-----------------------|--------------|
| 1 | Breakfast | Whole milk (glass) | 322 | 1108 |
| | | 2 pieces of fresh cheese (50 g) | 324 | |
| | Lunch | Whole milk (glass) | 322 | |
| | | 2 slices of mozzarella cheese (30 g) | 140 | |
| 2 | Breakfast | Whole milk (glass) | 322 | 1104 |
| | | 2 pieces of fresh cheese (50 g) | 324 | |
| | Lunch | 2 sardine units (50 g) | 219 | |
| | | 1½ bean ladle (160 g) | 109 | |
| | Snack | Yogurt | 130 | |
| 3 | Breakfast | Whole milk (glass) | 322 | 1115 |
| | | 2 pieces of mozzarella cheese (50 g) | 140 | |
| | Lunch | Cooked spinach (½ cup) | 112 | |
| | | Grilled sardines (2 units) | 219 | |
| | Snack | Whole milk (glass) | 322 | |
| 4 | Breakfast | Whole milk (glass) | 322 | 1112 |
| | | 2 Slices of prato cheese (30 g) | 282 | |
| | Lunch | Hake (100 g) | 378 | |
| | Snack | Yogurt | 130 | |

Note: Based on the Brazilian food composition table (2011).

Table 2. Food and types of meals.

Thus, men and women aged 19 to 50 years should intake 1,000 mg/day of calcium and from 51 years of age, both groups, 1,200 mg. Only patients in group B were instructed to use the menus at random, complying with the amount of calcium to be ingested daily. After total thyroidectomy and measurement of PTH 12 hours after surgery, a PTH value <15 pg/ml was considered to assess laboratory hypoparathyroidism. Patients with PTH ≥15 pg/ml were discharged on the first postoperative day and instructed to start prescription intake of calcium supplements in the presence of hypocalcemia symptoms and notify their physician (Figure 1).

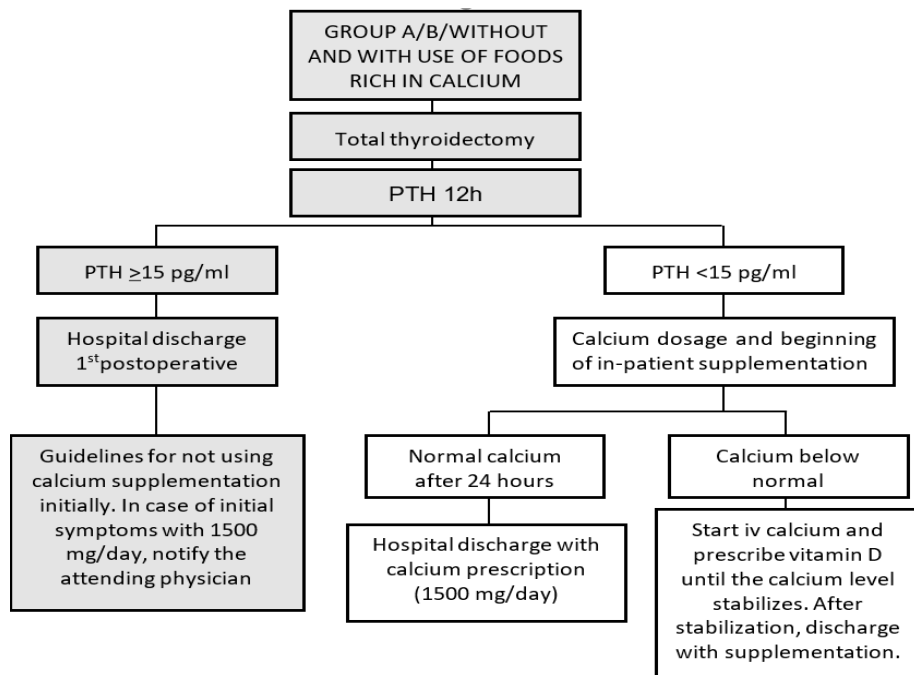


Figure 1: Algorithm for the use of i-PTH, 12 hours after total thyroidectomy, as suggestive of hypocalcemia.

All patients underwent TT. Parathyroids were not systematically searched for during surgery; only those that were within the surgical team's field of view were identified.

Statistical analysis

Exploratory data analysis was performed using measures called summary (mean, standard deviation, minimum, median, maximum, frequency and percentage) and charts construction. The groups were compared using the Mann-Whitney or Fisher's exact tests. To compare groups and times for PTH, ANOVA for repeated measures with PTH transformed into points was used. The significance level adopted was 5%. The SAS system for Windows (statistical analysis system), version 9.4 was used.

RESULTS

A total of thirty-one patients of both genders participated in this preliminary study, with a predominance of females; they were aged between 19 and 74 years, with a median of 49 years. The result of the anatomic pathology exam was benign in 68.7% of the cases; parathyroids were removed in 22.6% of the procedures (Table 3 and 4). In this work, a group comparison for categorical variables was performed (Table 5). As there were only two male patients, the groups were not compared from this standpoint. No significant differences were

found between the groups regarding pathological anatomy (p value=0.705), parathyroid removal(s) (p value=1.000) and PTH value <15 pg/ml (p value=0.119). This last variable (PTH) counts the number of patients who exhibit a 12-hour i-PTH less than 15 pg/ml. Table 6 shows PTH position and dispersion measurements by time of assessment (before and after total thyroidectomy surgery) as well as by group. To compare groups and times in relation to PTH, the ANOVA test was used. There was a significant difference of PTH values before and after surgery (p value <0.001) when compared with the groups. PTH values were lower after surgery in both groups, and more patients in group B (using calcium- rich foods) had $PTH \geq 15$ pg/ml.

Figure 2 shows the boxplots (box diagram) comparing times (before and after total thyroidectomy) and groups in relation to PTH. This figure is a graphical representation of Table 6, based on median data, indicating the parameters position and variation measurement. Likewise, we can see that, as mentioned, the PTH values were lower after surgery in both groups, with more patients in group B exhibiting a PTH value ≥ 15 pg/ml. The asterisk indicates the outlier. Patients in both groups remained hospitalized and were discharged based on the treatment flowchart used.

| Variables | N | Mean | Standard deviation | Minimum | Median | Maximum |
|-------------------------------|----|-------|--------------------|---------|--------|---------|
| Age | 31 | 49.90 | 14.57 | 19.00 | 49.00 | 74.00 |
| PTH (pre-operative) | 31 | 43.36 | 12.68 | 19.00 | 43.94 | 65.00 |
| TSH (pre-operative) | 31 | 2.48 | 1.92 | 0.01 | 1.80 | 6.48 |
| T4L (pre-operative) | 31 | 1.25 | 0.33 | 0.80 | 1.19 | 2.50 |
| Ionic calcium (pre-operative) | 31 | 1.21 | 0.06 | 1.08 | 1.21 | 1.35 |

Table 3: Measurement of position and dispersion of numerical variables considering the total group.

| Variables | Category | N | % |
|---------------------------------------|---------------------|----|------|
| Gender | Female | 29 | 93.6 |
| | Male | 2 | 6.4 |
| Anatomopathological | Goiter | 20 | 64.5 |
| | Papillary carcinoma | 10 | 32.3 |
| | Thyroiditis | 1 | 3.2 |
| Parathyroid removal(s) | 1 | 5 | 16.1 |
| | 2 | 1 | 3.2 |
| | 3 | 1 | 3.2 |
| | None | 24 | 77.4 |
| Without the use of calcium-rich foods | Group A | 18 | 58.1 |
| With the use of calcium-rich foods | Group B | 13 | 41.9 |

Table 4: Frequency distribution and percentage of categorical variables considering the total group.

| Variables | Category | Group A | | Group B | | P value |
|---------------------------------|---------------------|---------|-------|---------|--------|---------|
| | | N | % | N | % | |
| Gender | Female | 16 | 88.89 | 13 | 100.00 | NC |
| | Male | 2 | 11.11 | 0 | 0.00 | |
| Anatomopathological* | Goiter | 12 | 70.59 | 8 | 61.54 | 0.705 |
| | Papillary carcinoma | 5 | 29.41 | 5 | 38.46 | |
| Parathyroid withdrawal | 1+2+3 | 4 | 22.22 | 3 | 23.08 | 1.000 |
| | None | 14 | 77.78 | 10 | 76.92 | |
| PTH value/12 hours post-surgery | ≥15 | 6 | 33.3 | 8 | 61.54 | 0.119 |
| | <15 | 12 | 66.7 | 5 | 38.46 | |

Note: * The thyroiditis category has been deleted. because only one patient had this diagnosis.

Table 5: Frequency distribution and percentage of categorical variables by group and result of comparison between groups (Fisher's exact test).

| Time | Calcium group | N | Mean | Standard deviation | Minimum | Median | Maximum |
|-------------------------------|---------------|----|-------|--------------------|---------|--------|---------|
| Before surgery(PTH) | A | 18 | 42.98 | 11.81 | 19.00 | 44.66 | 65.00 |
| | B | 13 | 43.90 | 14.28 | 20.00 | 42.00 | 62.00 |
| After surgery (PTH-i/12 hour) | A | 18 | 14.93 | 15.62 | 2.87 | 7.53 | 62.27 |
| | B | 13 | 20.27 | 16.22 | 1.10 | 17.50 | 61.62 |

Table 6: PTH position and dispersion measurements by group and time (before and after total thyroidectomy surgery)- ANOVA test.

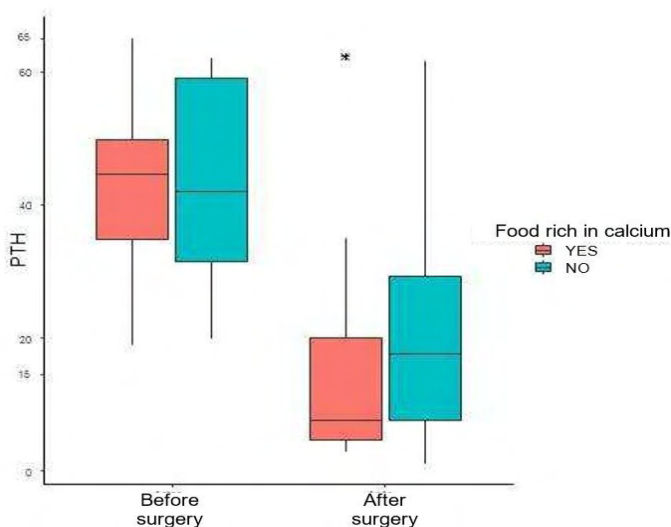


Figure 2: Boxplot of PTH by time (before and 12 hours after surgery) and by groups (with and without calcium- rich foods).

DISCUSSION

As there still seems to be no consensus as to when to perform the PTH

measurement after total thyroidectomy and which PTH value should be used as suggestive of hypoparathyroidism, a blood measurement was performed in both groups to compare the PTH result requested before the surgery with the 12 hours value after the aforementioned procedure. This time interval was based on works such as those by Graciano et al and Arer et al, who concluded in their analysis that this was a more specific period and also when referring to hemodilution.^{6,9,11} Regarding the PTH value used to suggest laboratory hypoparathyroidism in the postoperative period of total thyroidectomies, we considered the PTH value <15 pg/ml. This was based on the literature and on the PTH normality test of the PUCG laboratory (between 15 and 65 pg/ml).^{2,18,23,24}

Thus, hospital discharge, for both groups assessed, occurred only according to the post-surgery PTH test result according to the treatment flowchart used; such result should be between 15 and 65 pg/ml. Post-surgery calcemia was not measured as a function of the time in which calcemia concentration slumps.^{2,25}

Patients who met criteria for discharge on the first postoperative day were initially instructed not to use calcium supplementation. This instruction was also in line with the protocol of other authors.^{2,6,23} There was no significant difference between groups regarding inadvertent removal of parathyroid glands, which occurred in seven patients (22.6%). Campos et al reported that accidental parathyroidectomy is something common, that can occur in 6.4% to 31% of surgeries and that in their review they found 49% of parathyroid glands in intrathyroidal location, which makes their preservation impossible.²⁶ They reported a greater association of this condition with the papillary carcinoma diagnostic. This fact that was also observed in the study, showing that out of the seven patients in whom glands were identified in the surgical specimen, four (57.15%) were considered malignant.

In our study, we dealt with a small sample and with groups containing different number of individuals, but a difference in PTH values between the groups, measured before and after surgery, was observed. PTH values were smaller after surgery in both groups. But in the group that received calcium-rich foods, a greater number of patients exhibited $PTH \geq 15$ pg/ml.

All patients in our study underwent total thyroidectomies. However, other papers report patients who underwent total thyroidectomy and others who underwent partial thyroidectomy. Surgeries other than total thyroidectomy usually imply a lower risk of hypocalcemia.^{4,27,28}

The use of calcium-rich foods in the total thyroidectomy preoperative period and the potential influence on hypoparathyroidism rates have been evaluated. This was based on a few articles such as the one by Fauci et al who reports that there is a continuous exchange between plasma and bone calcium.²⁹ The calcium absorbed from the diet and that would cause an increase in this ion blood concentration is rapidly deposited in the bone tissues (bone remodeling-osteoblasts), and, in contrast, bone calcium is mobilized when its concentration in the blood decreases (osteoclasts). Heaney et al states that food is the best

source of calcium the body needs to maintain health.³⁰ Calcium-rich foods contain several other nutrients, which make them better suited than supplementing a mononutrient.

As thyroid surgeries have become more and more common, in addition to a standardized surgical technique, the search for new and effective methods that can reduce or alleviate the typical surgical complications of these operations should be considered.

Hypoparathyroidism can bring discomfort and risk to the person undergoing total thyroidectomy and, in more severe cases, in the presence of tetany, the manifestation of anxiety. In this preliminary study the use of evaluated calcium-rich foods administered before total thyroidectomy surgery, rather than the intake of tablets, suggested benefit to patients. An initial literature retrieval effort on this topic did not produce similar articles.

CONCLUSION

In this preliminary study, the assessment of calcium-rich foods used in the preoperative period of total thyroidectomy, according to the daily needs and according to the age group, suggested a reduction in the incidence of laboratory hypoparathyroidism. Patients who had $PTH \geq 15$ pg/ml were discharged safely on the first post-operative day and without the need for the initial use of calcium supplements.

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ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee

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