

High urinary output as a predictor of hypoparathyroidism post total-thyroidectomy

Gasto urinario alto como predictor de hipoparatiroidismo tras tiroidectomía total

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Abstract

Objective: to determine the usefulness of high urine output as a low-cost early predictor for postoperative hypoparathyroidism. **Method:** A study was conducted inside The American British Cowdray Medical Center I.A.P. for a year in adult patients who underwent total thyroidectomy divided in two groups: those with post-surgical hypocalcemia and without post-surgical hypocalcemia using the 24-hour calcium levels. Urinary output of each patient was verified searching for the relation between this measurement and the probability of developing post-surgical hypoparathyroidism. **Results:** A total of 47 patients were studied, of whom 19 (40%) were classified with post-surgical hypocalcemia and 28 (59.5%) with no post-surgical hypocalcemia. The urinary output mean on the first 8 hours post-operative was higher in the post-surgical hypocalcemia group in comparison with the group with no evidence of hypocalcemia, showing no significant difference ($p = 0.392$). Urinary output 16 hours post-surgical was no significant either ($p = 0.435$). **Conclusions:** In our study, there was no relation found between the increase of the urinary output and the post-surgical hypoparathyroidism prediction. Further studies with a bigger sample and a stronger methodologic design (prospective) are needed to determine if the difference obtained may be useful as a predictor.

Keywords: Hypocalcemia. Hypoparathyroidism. Parathormone. Thyroidectomy.

Resumen

Objetivo: Determinar la utilidad del gasto urinario alto como predictor temprano de bajo costo para hipoparatiroidismo posoperatorio. **Método:** Se realizó un estudio retrospectivo unicéntrico a 1 año en adultos sometidos a tiroidectomía total en The American British Cowdray Medical Center I.A.P., calculando el gasto urinario en 24 horas, utilizando valores de calcio sérico corregido por albúmina con una tabla de correlación e identificando a los pacientes que recibieron calcio suplementario en las primeras horas de posoperatorio. Se dividieron en pacientes con hipoparatiroidismo posoperatorio y con valores normales de calcio en el primer día, diferenciando a los que recibieron suplementación oral de calcio profiláctico. **Resultados:** Se estudiaron 47 pacientes, 19 (40%) en el grupo con hipocalcemia posoperatoria y 28 (59.5%) en el grupo sin hipocalcemia posoperatoria. La media de gasto urinario en las primeras 8 horas de posoperatorio fue mayor en el grupo de hipocalcemia posoperatoria en comparación con el grupo sin hipocalcemia, sin diferencia significativa ($p = 0.392$), y tampoco durante las primeras 16 horas ($p = 0.435$). **Conclusiones:** En nuestro estudio no existe relación entre el incremento del gasto urinario y la predicción de hipoparatiroidismo posoperatorio. Se necesitan estudios con muestras de mayor tamaño y con un diseño metodológico más fuerte (prospectivo) para determinar si en realidad la diferencia obtenida puede figurar como predictor.

Palabras clave: Hipocalcemia. Hipoparatiroidismo. Hormona paratiroidea. Tiroidectomía.

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Date of reception: 24-06-2020
Date of acceptance: 25-08-2020
DOI: 10.24875/CIRUE.M23000354

Cir Cir (Eng). 2021;89(4):485-489
Contents available at PubMed
www.cirugiaycirujanos.com

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Introduction

Thyroid surgery represents one of the most common elective surgeries around the world; in Germany alone, nearly 60,000 thyroidectomies are practiced annually¹. Although transoperative complications are low and mortality is negligible, postsurgical hypoparathyroidism (PoSH) is the most common postoperative complication of total thyroidectomy².

Currently, there is no international consensus on the definition of PoSH, which is why establishing its exact incidence is complicated. In a systematic review of 115 studies, a temporary incidence of PoSH of 27% was obtained³, and 23.6% in 2017 according to the British Association of Endocrine and Thyroid Surgeons (BAETS), which proposes the definition of PoSH as a serum calcium value < 8.4 mg/dL on first postoperative day⁴, which will be used for the purposes of this study.

In 2010, the Thyroid Cancer Alliance reported a follow-up of 1,995 thyroidectomy post-operated patients, among whom up to 39% had transient PoSH, with progression to permanent PoSH in 14%⁵.

The origin of PoSH is mainly by direct injury to the parathyroid glands through compromising their vascular supply during thyroidectomy, which results in hypoxia of one or more parathyroid glands, a phenomenon known as stunning, which causes a decrease in serum concentrations of parathyroid hormone (PTH), calcium, phosphorus and magnesium⁶.

It is a well-known fact that hypocalcemia often exhibits a delay of up to 24 hours in comparison with PTH decline, due to calcium physiology and its binding to proteins and, therefore, predictive strategies have been proposed for early recognition (intact serum PTH determination, with a decrease below 10 pg/mL at 4 hours post-surgery positively predicting the occurrence of PoSH with a sensitivity of 94% and specificity of 100%)⁷.

The purpose of this study is to search for low-cost early predictors following the physiological principle of PTH renal action for inducing a higher expression of cell surface calcium transient receptor subfamily V members 5 and 6 (TRPV5 and TRPV6), which are highly sensitive to calcium⁸, which allows passive entry to the cell by gradient difference. Calcium must pass to the peritubular fluid through the basolateral membrane via $\text{Na}^+/\text{Ca}^{++}$ anti-transporter (NCX1) and Ca^{++} ATPase (PMCA), which in turn are activated by PTH indirect action⁹.

Absence of the aforementioned hormonal stimulus in the context of PoSH results in a decrease in calcium uptake at the distal tubule, with $\text{Na}^+/\text{Ca}^{++}$ exchange ceasing to occur in the basolateral membrane of the cell and causing low sodium intracellular concentration and, therefore, lower intracellular oncotic force at distal tubule and, finally, less water absorption and increased urine output.

Method

Design

A retrospective, single-center 1-year study was carried out at The American British Cowdray Medical Center I.A.P. in adults aged 18-99 years, both males and females, who had undergone total thyroidectomy between January 1, 2018 and December 31, 2018.

Inclusion criteria

Patients who underwent total thyroidectomy with or without central compartment or lateral compartments dissection.

Exclusion criteria

- Patients with serum albumin abnormal levels (normal range: 3.4-4.8 g/dL).
- Patients with preoperative serum calcium abnormal levels (normal range: 8.8-10.2 mg/dL).
- Patients with preoperative PTH abnormal values (normal range: 9.5-75 pg/mL).
- Patients with renal insufficiency.
- Patients without postoperative calcium intake.
- Patients without diuresis quantification at immediate postoperative period.

Immediate postoperative period diuresis records of the first 8, 16 and 24 hours were verified, and urine outputs of each patient were calculated, using the albumin-corrected serum calcium values of each patient in order to enable the generation of a correlation table. Patients who received supplemental calcium within the first postoperative hours were identified.

Statistical analysis

The patients were divided in two groups: those who developed PoSH and those with normal calcium values at first postoperative day. Urine output of the first

8 hours was analyzed in both groups, and hypoparathyroidism was determined with BAETS parameters (serum calcium < 8.4 mg/dL on postoperative day 1).

Similarly, a distinction was made between those patients who received prophylactic oral calcium supplementation.

The Kolmogorov-Smirnov test was used to corroborate the urine output variable normality; however, non-normal distribution was identified in the postoperative hypocalcemia group and borderline normal distribution in the group without postoperative hypocalcemia, which is why Mann-Whitney's U-test for two independent variables was used, with IBM SPSS Statistics Subscription 25 software being employed.

The odds ratio is presented with a 95% confidence interval, and a p-value < 0.05 was regarded as significant.

Results

The medical records from 73 patients who underwent total thyroidectomy during 2018 at The American British Cowdray Medical Center I.A.P. were collected, out of whom 47 subjects met the inclusion criteria: 40% made up the group with postoperative hypocalcemia, and 59.5%, the group without postoperative hypocalcemia.

In both groups, the female gender was predominant: 79% in the postoperative hypocalcemia group and 78% in the group without postoperative hypocalcemia.

Mean age in the group of patients with postoperative hypocalcemia was lower (45 years) than that in the group without hypocalcemia (50 years), with no significant difference ($p = 0.332$) for being regarded as a risk factor. Similarly, the age group with the highest prevalence of postoperative hypocalcemia was the 41-60-year group (41%).

Mean urine output within the first 8 postoperative hours was higher in the postoperative hypocalcemia group (1.61 ± 0.25 mL/kg/h) than in the group without hypocalcemia (1.21 ± 0.13 mL/kg/h) (Fig. 1); however, the difference was not significant ($p = 0.392$). No significant difference was identified either on first 16 hours urine output ($p = 0.435$).

Similarly, 24-hour urine output was higher in the postoperative hypocalcemia group (2.07 ± 0.32 mL/kg/h) than in the group without hypocalcemia (1.87 ± 0.20 mL/kg/h), although, again, the difference was not significant ($p = 0.501$) (Fig. 2).

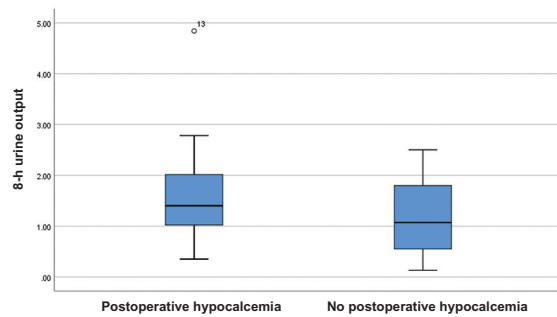


Figure 1. Comparison of urine output 8 hours after total thyroidectomy in patients with and without postoperative hypocalcemia ($p = 0.392$).

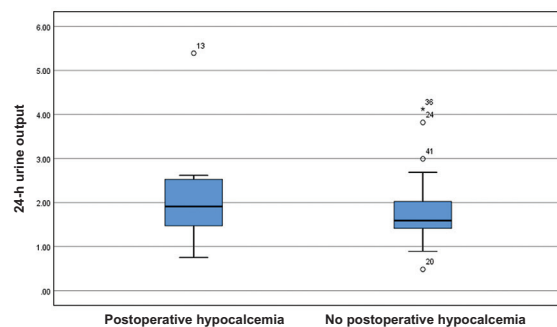


Figure 2. Comparison of urinary output 24 hours after total thyroidectomy in patients with and without postoperative hypocalcemia ($p = 0.501$).

In both groups, 36.1% of patients (17) received calcium supplementation within the first postoperative hours, out of whom 41% had postoperative hypocalcemia in spite of this, while in the group without postoperative hypocalcemia 64.2% of patients (18) did not receive calcium supplementation. Therefore, a positive correlation between calcium supplementation and postoperative hypocalcemia prevention could not be obtained ($p = 0.938$).

Mean hospital stay was longer in the group with postoperative hypocalcemia, with an average of 2.68 days, in comparison with 1.82 days in the group without postoperative hypocalcemia, with this difference being statistically significant ($p = 0.020$).

Discussion

Currently, there is no internationally-accepted consensus on the definition of PoSH. Variability in the definitions is such that Mehanna et al.¹⁰ found incidence rates of 0% to 46% in the same cohort of patients depending on the definition that was used.

Lorente-Poch et al.¹¹ adopted the term “parathyroid failure” in order to include three syndromes; for the purposes of this study, the first one was used as parameter: postoperative hypocalcemia (serum calcium < 8 mg/dL within the first 24 postoperative hours, with calcium supplementation being required at hospital discharge).

The importance of this phenomenon lies in its substantial incidence, the morbidity it entails, taking as example the high costs involved: hospital stay in our study exceeded 24 hours ($p = 0.20$). In one study, a survey was conducted on 374 patients with permanent PoSH, among whom 75% currently have symptoms despite receiving proper treatment, 80% had attended the emergency department or had been hospitalized at least once as a consequence of PoSH, which is why we highlight the important investment that continues to be made in the long term as a consequence of this pathology¹¹.

Mokrysheva et al.¹² gave follow-up to 76 patients with permanent PoSH for 2 years (2017-2019), and found that the most common complications were nephrolithiasis in 22%, glomerular filtration rate decrease below 60 mL/min/1.73 m² in 11%, arrhythmias and corrected-QT prolongation in 5 patients (6.5%), as well as Fahr syndrome (6.5%), characterized by central nervous system calcifications.

Among the attempts to predict this phenomenon, Barczyński et al.¹³ reported that intact PTH decrease at the time of skin closure, and at 4 hours (< 10 pg/mL) post-surgery is significantly correlated with the onset of postoperative hypocalcemia at 24 hours, with a positive predictive value of 90%. Subsequently, this fact was corroborated by different authors^{14,15}. In turn, Sieniawski et al.¹⁶, in a prospective study of 142 patients undergoing total thyroidectomy for benign disease, concluded that the factor with the highest positive predictive value was a PTH decrease at 6 hours of more than 65% with regard to baseline value ($p = 0.001$).

In 2014, a systematic analysis showed that the absence of a decrease in calcium concentration on 24-hour serial measurements has a poor predictive value for predicting transient hypocalcemia¹⁷.

In turn, our study sought to identify urine output increase as a predictor of PoSH. Urine output in the PoSH group was found to be higher in all measurements (at 6, 8 and 24 hours), but no significant difference was found in any measurement.

The surgical technique is considered to be an important factor, since it appears to influence the

likelihood of developing PoSH. In 2017, Chen et al.¹⁸ published a study in which they analyzed 9-year PoSH cumulative incidence by evaluating six different thyroidectomy procedures in 9,315 patients, and demonstrated that bilateral subtotal thyroidectomy had the highest PoSH incidence (13.5%), while unilateral subtotal thyroidectomy had the lowest incidence (1.2%), which indicates that aggressiveness of the procedure is correlated with the occurrence of PoSH.

In the context of prolonged hypoparathyroidism, the predicting factors that have been found to be most clearly associated are the dose of calcium or calcitriol received at hospital discharge and the presence of high serum calcium values together with low, but detectable values of intact PTH at one month post-surgery¹⁹.

Similarly, it was not possible to find a significant correlation between age and the development of PoSH, as it has been reported by other authors²⁰; however, the age group with the highest incidence of PoSH in our study was found to be that of 41-60 years.

As described in the international literature, the female gender was predominant in our sample, but, given the number of male cases, there is a bias for determining if patient gender might be significantly correlated with the rate of postoperative hypocalcemia in our study.

The effects of the use of calcium, vitamin D and PTH in the management of PoSH have been previously investigated. Edafe et al.²¹ carried out a review of 1,751 publications to examine the effects of administering these elements; however, it was concluded that there is no high-quality evidence for short- and long-term management of hypoparathyroidism after total thyroidectomy, which is why an analysis could not be performed, and the authors concluded that there is no high-quality evidence for the prevention of PoSH with these measures. In our study, vitamin D and calcium supplementation in the immediate postoperative period did not reflect a significant difference in the incidence of postoperative hypocalcemia.

Conclusions

Parathyroid failure represents a real challenge for the surgeon. Despite the different predictors that have been proposed for timely management of postoperative hypocalcemia, emphasis should be made on systematically using a particular surgical technique, with an emphasis on subcapsular dissection and inferior thyroid artery identification in order to

improve parathyroid glands in situ preservation during total thyroidectomy.

Urine output increase in our study was not significantly correlated with the postoperative hypocalcemia group, despite having documented that urine output in the postoperative hypocalcemia group was indeed higher. Studies with a larger sample size and more robust methodological design are needed in order to determine whether this difference can actually serve as a predictor.

Conflicts of interest

No author declares having conflicts of interest.

Funding

There was no funding of any kind for this study.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments have been performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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